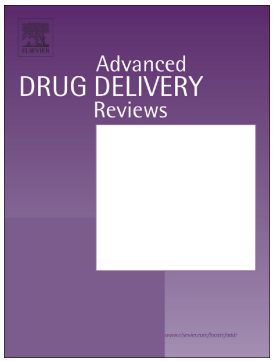
Cell Encapsulation: Overcoming Barriers in Cell Transplantation in Diabetes and Beyond



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Cell Encapsulation: Overcoming Barriers in Cell Transplantation in Diabetes and Beyond

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Abstract
Cell-based therapy is emerging as a promising strategy for treating a wide range of human diseases, such as diabetes, blood disorders, acute liver failure, spinal cord injury, and several types of cancer. Pancreatic islets, blood cells, hepatocytes, and stem cells are among the many cell types currently used for this strategy. The encapsulation of these "therapeutic" cells is under intense investigation to not only prevent immune rejection but also provide a controlled and supportive environment so they can function effectively. Some of the advanced encapsulation systems provide active agents to the cells and enable a complete retrieval of the graft in the case of an adverse body reaction. Here, we review various encapsulation strategies developed in academic and industrial settings, including the state-of-the-art technologies in advanced preclinical phases as well as those undergoing clinical trials, and assess their advantages and challenges. We also emphasize the importance of stimulus-responsive encapsulated cell systems that provide a "smart and live" therapeutic delivery to overcome barriers in cell transplantation as well as their use in patients.

1. Cell-Based Therapy

Cell-based therapy consists of implanting or delivering living cells or sustaining their development in a patient for the treatment of a certain disease or condition [1]. In contrast to small-molecule drugs and biologics such as engineered proteins and antibodies, which are the predominant treatment modalities for most diseases, cell-based therapy delivers complex living entities that are capable of modulating their functions and sensing and responding to their environment. The migratory and proliferative capacity and production of cells, the delivery of therapeutics, and the intercellular interactions are some of the characteristics that can be manipulated to address the ongoing challenges in various pathologies, including diabetes, cancer, spinal cord injuries, and autoimmune and neurodegenerative diseases [2,3]. For example, in the treatment of osteoarthritis, the conventional treatment comprising opioids and nonsteroidal anti-inflammatory drugs provides pain relief but not the restoration of damaged tissue. By contrast, cell therapies utilizing induced pluripotent stem cells (iPSCs) or autologous chondrocytes repair the damaged cartilage and tissues. Transplantation of these cells may thus become a standard treatment option and is predicted to replace whole organ transplants in certain cases, such as in the treatment of diabetes and liver failure [4,5].

The adoption of cells for therapeutic purposes has evolved dramatically, beginning with blood transfusions in the 1600s [6], renal transplantation in animal models by Dr. Emerich Ulmannn in

1902 [7,8], and blood vessel and organ transplantation by Drs. Alexis Carrel and Charles Guthrie in the early 1900s [9]. Early pioneering developments in cell transplantation included injections of ox parathyroid cells in human patients in 1931 and lyophilized cells in 1949 by Dr. Paul Niehans [10] and the transplantation of islets encapsulated in semipermeable microcapsules by Dr. Thomas M. S. Chang in 1964 [11]. Today, cell types from different sources are being evaluated in personalized approaches for treating a number of diseases.

Currently, one of the most researched areas in cell transplantation is diabetes, which continues to increase in prevalence. Type 1 diabetes mellitus (T1DM) is an autoimmune disease where insulin-producing beta cells are destroyed by body's own immune system leading to significant reduction in insulin production. The cause of this attack is still being researched, however scientists believe that a genetic predisposition and an environmental trigger like a virus attack play important roles. Type 2 diabetes has several causes of which genetics and lifestyle are the key contributing factors. A combination of these factors can cause insulin resistance, where despite insulin secretion, the body is unresponsive to insulin, leading to high blood glucose levels. In models of early diabetes, beta cells exposed to increased glucose levels develop abnormalities in glucose stimulated insulin secretion. The beta cells also undergo de-differentiation, with changes in gene expression and in structural and functional characteristics. Persistent hyperglycemia or exposure to high levels of free fatty acids (FFA) can lead to further dysregulation of insulin secretion, beta cell apoptosis and self-perpetuating reduction in functional beta cell mass. As a result, exogenous insulin is required to be administered to the patients for survival.
Despite significant advances in the treatment of T1DM, the management of the disease remains suboptimal and is linked to chronic complications, comorbidity and mortality even in individuals at a relatively young age. Whole-pancreas transplantation has shown to prevent chronic complications and result in adequate glycemic control. However, the invasiveness of the intervention, post-surgical morbidity and high mortality are still of concern [12–14]. To address the continuous treatment need for "brittle T1DM" patients, intravascular cell infusion transplanting allogenic pancreatic islets was developed as a better alternative [15].

Pancreatic islet transplantation was first attempted in 1893 [16]. It took 80 years to demonstrate an acceptable rate of success, in the absence of an immune barrier (i.e., using autografts) [17,18] . In the 1980s, several autotransplant trials were performed extracting islets from the patient's own pancreas and infusing them into the liver via the portal vein. Unfortunately, insulin independence was achieved in only 10% of patients in these early trials [19,20]. The success of this approach was significantly improved by the development of the Edmonton protocol at the University of Alberta in 2000. . In this procedure, Shapiro and colleagues purified pancreatic islets isolated from the pancreas of a brain-dead donor. Next, using fluoroscopic guidance system to guide catheter placement, 4000 islet equivalents per kilogram of the recipient's body weight were infused within the main portal vein. To prevent immune rejection of the transplanted islets, the group developed a glucocorticoid-free immunosuppressive protocol that included sirolimus, low-dose tacrolimus, and a monoclonal antibody against the interleukin-2 receptor (daclizumab). Although most previous islet transplantations have been performed in combination with kidney transplantation, the procedure was limited only to islet transplantation alone [21].

In the NCT00706420 trial, all treated patients with T1DM (7) gained insulin independence and retained it for 12 months post-transplant [21]. Since then, human pancreatic islet transplantation has transitioned from a rare experimental protocol to a routine and safe clinical procedure, with over 1,500 interventions performed worldwide (1,011 allogeneic transplants and 660 autologous transplants according to the Collaborative Islet Transplant Registry [CITR]). A 12-year follow-up

of seven patients from the 2000 study found that the transplanted islets remained functional [22], with one patient maintaining insulin independence without the need for supplemental diabetic medication or transplants; another patient was insulin independent for 10.9 years, and three patients received subsequent islet transplants. At the end of the study, two patients were insulin independent, whereas insulin was being administered to five patients. This study demonstrated the long-term safety of islet transplantation, as there were no adverse infections, hypoglycemia, or lymphoma observed in the patients.

The establishment of the Edmonton protocol for islet autotransplantation represents an outstanding advance in the field. However, its success has been challenged over the years by the dispersion of islets in the portal vein postinjection and the limited number of viable islets that can be retrieved from the patient. Whereas the first issue is a topic of research, the need for additional cell sources has prompted the use of allogenic or xenogeneic cells from donors. This requires combating immune rejection of the transplant and the ensuing need for lifelong immunosuppressive treatments, which significantly reduce the patient's quality of life [23]. One of the first attempts to solve this problem was by Drs. Prehn, Weaver, and Algire in 1954. Using immunized mice, they demonstrated that transplanted homologous (allogeneic) cells did not trigger an immune response when encapsulated by a porous membrane and administered to the peritoneal cavity [24]. Encouraged by this result, several research groups have extensively investigated semipermeable membranes as a physical means to immunoisolate the transplant graft and abrogate immune rejection [25,26]. More recently, biological approaches involving the genetic manipulation of transplant cells have been researched as a strategy to eliminate the need for systemic immune suppression regimens [27–31].

The general objective of encapsulation materials or devices is to compartmentalize the transplanted cells within a protected environment to promote their long-term viability and functioning as an artificial organ. These systems need to allow for the bidirectional transport of oxygen and metabolic products as well as the real-time and unobstructed release of therapeutic agents, such as hormones or enzymes, in response to external biological stimuli [32–34]. These functional requirements necessitate the consideration of physical parameters, such as porosity, rigidity, tortuosity, chemical composition, and surface functionalization of membranes, as well as the ability of the device to be refilled and replaced, for engineering an effective encapsulation technology [23,35]. The breadth of requirements has led to a surge in the testing of synthetic and bio-based materials as means of encapsulating a wide variety of cell types. Present day strategies comprise implantable, personalized, and multifunctional living cell factories that are capable of providing immune protection and enabling a controlled and continuous delivery of therapeutics. These structures can house a vast array of cell types, such as the patient's own cells and animal-derived and engineered cells, by synergistically leveraging genetic and bioengineering technologies, material science, and nanotechnology [36–38].

Cell-based therapy has changed the treatment paradigms for many diseases, including some that were considered incurable, such as diabetes. It is already established as a standard-of-care treatment and is reimbursable by insurance companies or covered by national health systems in several countries. Given the increasing rates of diabetes worldwide, the approval of an islet-based therapy is an opportunity for cell therapeutics to progress beyond an investigative niche arena towards a globally recognized standard of care [5]. Cell transplantation is also being used or explored for the treatment of other pathologies (Fig. 1). A plethora of cell types from autologous, allogeneic, or xenogeneic sources—stem cells (neural, mesenchymal, induced pluripotent), pancreatic islets, fibroblasts, and renal proximal tubule cells—is being tested for treating different diseases, such as neurodegenerative and chronic eye diseases, cancer, diabetes, cardiovascular diseases, wound regeneration, and renal failure [39–44]. Ideally, upon

encapsulation and implantation at a specific site in the body, these cells should function in the same manner as the native organ.

In this review, we describe various encapsulation strategies, including the state-of-the-art technologies at advanced preclinical phases and those undergoing clinical trials for diabetes and other diseases. First, we introduce the types of cells used in cell transplantation, highlighting their various sources and applications. Second, we describe current strategies of cell microencapsulation and macroencapsulation in diabetes and assess their advantages and challenges. We also highlight the importance of “smart” (stimulus-responsive and “live”) encapsulated cell systems in overcoming obstacles in cell transplantation and their use for cell delivery in patients. Third, we describe the applications of encapsulated cell therapies in other pathologies, such as chronic eye diseases (age-related macular degeneration and diabetic retinopathy), neurodegenerative diseases (Alzheimer’s and Parkinson’s), several types of cancer, chronic wounds (venous leg ulcers and diabetic foot ulcers), cardiovascular diseases (myocardial infarction [MI]), and renal diseases (acute kidney injury and end stage renal disease).

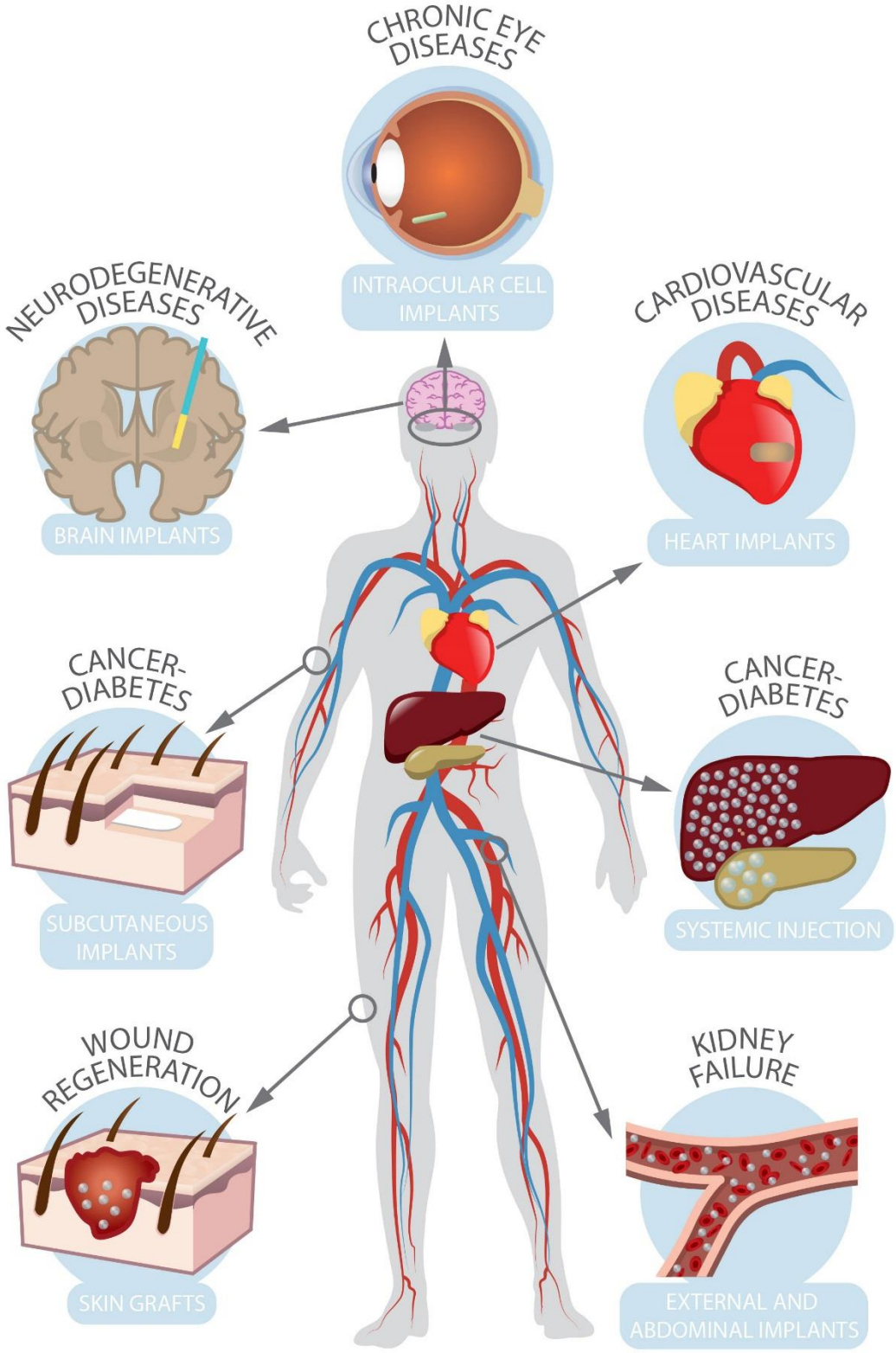

***Figure 1**: Schematic diagram of various representative strategies and cell types under advanced preclinical and clinical development, where cells, upon encapsulation and implantation, are used to restore or mimic and replace the functions of the diseased organs.*

2. Cell Types

The cell type chosen for transplantation depends mainly on the pathology treated and the organ targeted. Those selected are typically cells that secrete therapeutic antibodies and hormones and aid in the regeneration of damaged or defective tissues. The viability of cells and their controlled release of therapeutic factors are essential for establishing long-term function and an efficient therapy. The cell source could be autologous, allogeneic, or xenogeneic. The therapeutic potential of cell transplantation for many chronic conditions has led to a greater demand for high-quality cells, resulting in the development of innovative tissue engineering strategies for stem cell-derived therapeutic cells and the evaluation of animal-derived cells. Although xenografts from nonhuman primates (NHP) are physiologically and immunogenically compatible with humans, apes are endangered and the use of NHP cells raises ethical concerns. Thus, pigs are the next alternative species of choice [45]. In addition to primary and genetically engineered cells, artificial cell-like structures, such as polymersomes, have also been investigated for therapeutic use [27,30]. Some of the most widely tested cell types for transplantation are summarized below (Fig. 2).

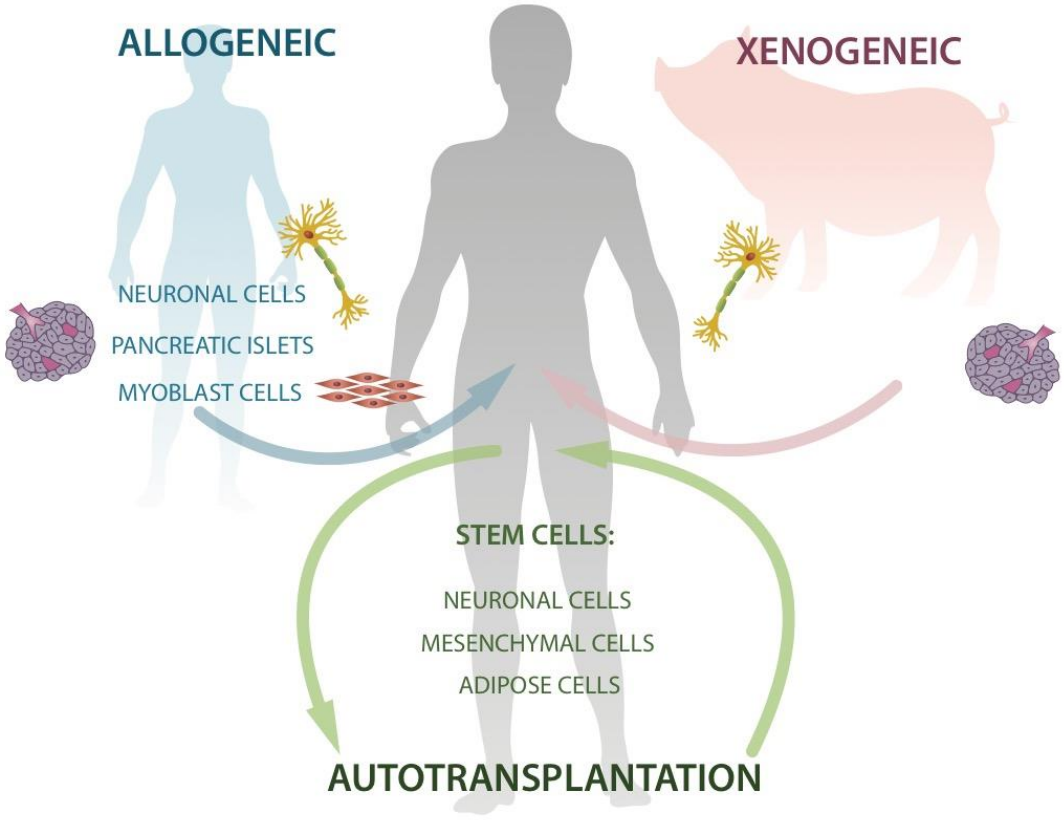

Figure 2: *Cell sources for cell therapy applications.*

2.1. Cells for allogeneic or xenogeneic transplantation

A variety of human and animal cell types have been evaluated for therapeutic transplantation into humans. Although detailed descriptions of these are beyond the scope of this review, several cell types that are being investigated in advanced preclinical or clinical studies are described below.

2.1.1. Pancreatic islets

Pancreatic islets or islets of Langerhans, named after the German physician Paul Langerhans, are responsible for endocrine function of the pancreas. Normal human pancreas contains approximately 1 million islets, consisting of mainly four different types of cells. The predominant cell type, beta cells, produce the hormone insulin, which promotes cellular uptake and metabolism of glucose. It prevents release of glucose by the liver, causes uptake of amino acids by muscle cells and inhibits the breakdown and release of fats. The inability of the islet cells to produce insulin or the failure of the body's cells to respond to insulin will lead to high blood glucose levels causing diabetes mellitus. On the contrary, the alpha cells of the islets of Langerhans produce the hormone glucagon, which cause release of glucose from the liver as well as fatty acids from fat tissue. The third cell type, delta cells, produce somatostatin, a strong inhibitor of somatotropin, insulin, and glucagon; its role in metabolic regulation is not yet clear. A fourth cell type, PP cells, located at the periphery of islets, secrete pancreatic polypeptide. Human islets have a unique architecture allowing all endocrine cells to be adjacent to blood vessels and permitting heterologous contacts between beta and alpha cells, and homologous contacts between beta cells. The hormones regulate the secretion of one another through paracrine cell to cell interactions and play a crucial role in maintaining homeostasis.

When pancreatic beta cell function is severely compromised as in the case of T1DM, insulin replacement or islet transplantation remains the only treatment option. Pancreatic islets harvested from human cadaveric donors and transplanted via portal vein injection have been shown to be a valuable alternative to frequent administration of insulin injections to treat T1DM. However, due to the poor yield of harvesting protocols, islets from multiple (2 to 4) donors are required to achieve insulin independence. Further, challenges associated with immune suppression, and loss of viability and function over time remain significant hurdles to improve transplantation outcomes [46]. As such, immune segregation for islet transplants has been widely studied with materials such as alginate, chitosan, agarose, gelatin and other polymeric materials as wells macro scale devices [47]. Detailed descriptions of these encapsulation systems are provided in subsequent sections of this review. Several clinical trials for assessing the safety, metabolic and immune responses have been performed or are ongoing for alginate encapsulated human beta cells (NCT00790257, NCT00790257), and macroencapsulated human islets (NCT02064309). In an attempt to improve islet availability, other sources have been explored. Porcine insulin differs from human insulin by only a single amino acid, and pigs are considered a suitable choice for harvesting islets from a xenogeneic source [45,48]. In light of this, porcine islets encapsulated in agarose are being investigated for clinical use [49].

2.1.2. Myoblasts

For the therapeutic delivery of proteins for skeletal muscle regeneration, preclinical studies are investigating encapsulated muscle cells (myoblasts). Puicher *et al.* [50] showed that genetically engineered murine myoblasts could be used in the treatment of Hurler's syndrome—also known as mucopolysaccharidosis type I. In their study, C2C12 cells that were transfected to secrete high levels of lysosomal enzyme α-L-iduronidase were encapsulated in alginate microcapsules and implanted intraperitoneally in mice, resulting in increases in enzyme activity and decreases in glycosaminoglycan activity for up to 3 months. In a study by Lathuilière *et al*. [51], C2C12 murine myoblast cells that were infected with lentiviral vectors to express firefly luciferase were encapsulated in polymeric flat-sheet macrodevices and implanted subcutaneously in the dorsa of mice. The density of the injected cells, the porosity of the permeable membrane, and the stiffness of the hydrogel used for encapsulation were tuned to achieve prolonged cell viability and delivery of recombinant proteins *in vivo* [51]. The same research group showed that myoblasts genetically engineered to express anti-amyloid-β antibodies and that were encapsulated in the flat-sheet device could be used for the treatment of Alzheimer's disease

[52]. Three-dimensional (3D)-bioprinted constructs comprising myoblast cells have been shown to mimic skeletal muscle tissue *in vitro* and *in vivo*. The implantation of these bioartificial constructs in mice has shown promise for muscle tissue regeneration and reconstruction [53]. These studies serve as pioneering proof of concepts for the allogenic implantation of myoblast cells for the prolonged therapeutic delivery of proteins and as a cost-effective alternative to recombinant protein therapy, as well as for tissue regeneration [51–54].

2.1.3. Choroid plexus

The highly active and vascularized cluster of epithelial cells situated in the blood–cerebrospinal fluid barrier—the choroid plexus—is responsible for the maintenance of brain homeostasis, the production of cerebrospinal fluid, the detection and transmission of immune signals [55,56], and the clearance of toxic agents from the brain [57]. The encapsulation of cells of the choroid plexus is under study for the treatment of aging disorders, cochlear [58,59] and neurodegenerative diseases [60], chronic wounds [61], and Huntington's disease [62]. Furthermore, it is being clinically tested for the treatment of Parkinson's disease (NCT01734733) [63,64], owing to the abundance of trophic and regenerative components in the choroid plexus and its ability to adapt and function in different microenvironments [61]. Borlongan *et al.* [62] demonstrated that implanted alginate-encapsulated choroid plexus cells were able to release neurotrophic factors and protect striatal neurons from damage in a rodent model of Huntington's disease. Later, the same group showed that alginate-encapsulated porcine xenografts provided structural and functional neuroprotection in a rodent model of stroke [65]. Luo *et al.* [66] demonstrated the neuroprotective efficacy of alginate-encapsulated porcine choroid plexus cells in an NHP model of Parkinson's disease, without the need for immunosuppressant drugs. These notable examples demonstrate the great clinical potential of encapsulated choroid plexus cells for delivering multiple neurotrophic agents to provide structural and functional protection in various neurodegenerative and traumatic conditions.

2.2. Cells for autologous transplantation

Patient-derived cells for transplantation are cells either harvested from the native organ, as in the case trauma or surgical removal (e.g., for pancreatectomy), or differentiated from stem cells via specific protocols. The various autologous cell types are presented below, with a particular emphasis given to stem cells, due to their largely untapped potential for managing various diseases.

2.2.1. Pancreatic islets

The transplantation of autologous pancreatic islets is typically performed when a patient with chronic pancreatitis undergoes a total pancreatectomy for intractable pain that is not controllable with medical treatment. The cells are isolated from the patient's own pancreas and transplanted back through the portal vein. Since its first clinical application by researchers at the University of Minnesota School of Medicine in 1977, advances in cell isolation and purification have improved islet autotransplant outcomes and expanded its clinical use [67]. However, only a few clinical centers in the United States are performing this procedure, and there is no available information on its worldwide use. Although the clinical outcome depends on the yield of islets and approximately 70% of patients require long-term insulin therapy after surgery, most patients still benefit from functioning islets and a simpler management of diabetes.

2.2.2. Stem cells

Stem cell therapy has advanced as the treatment option for a number of diseases, including cardiovascular, neurological, degenerative, and autoimmune diseases, blood and bone marrow cancers, burns, corneal damage, and organ failure. Stem cells are a potentially unlimited source of various therapeutic cell types [68]. With the possibility of reversing diabetes with islet

transplantation and the insufficient supply of islets from donors, there are increasing efforts to generate functional insulin-producing beta-like cells from stem cells. Several protocols have been developed to systematically guide the differentiation of human embryonic stem cells, and more recently, iPSCs, into pancreatic endoderm. Pancreatic endoderm cells have been shown to mature *in vivo* and function similarly to beta cells for prolonged periods following transplantation. In other cases, cells are transplanted after fully differentiating into beta cells *in vitro*. The results with these methods are encouraging, and recent efforts are directed towards improving the differentiation conditions, the expansion of cells at specific progenitor stages, and the purification of target cell populations to obtain sufficient quantities of functional pancreatic beta-like cells. There are approximately 6,000 clinical studies utilizing stem cells currently registered, some of which utilize encapsulated stem cells, such as ViaCyte PEC-01^{TM} macroencapsulated stem cell-derived beta cells. However, the challenges related to graft vascularization and viability and the uncertainty about their long-term fate in the host body, including teratoma formation, need to be addressed prior to their routine clinical use. Many research groups are utilizing various strategies to address these challenges, which are discussed in detail in section 3.4.2.

*2.2.3 Human embryonic stem cell-derived beta cells: I*n a preclinical study, glucose-responsive human embryonic stem cell-derived mature beta cells encapsulated in alginate derivatives and implanted in the intraperitoneal cavities of mice were shown to promote glycemic correction and survival, even 174 days after delivery without immunosuppressive treatment [69]. ViaCyte PEC-01^{TM} cells encapsulated in the Encaptra® drug delivery system are under rapid development for the treatment of type 1 and type 2 diabetes. After subcutaneous implantation, the beta cell precursors further differentiate into mature insulin-secreting cells that control blood glucose levels.

2.2.4 Pluripotent stem cells (PSCs): PSCs have the ability to self-renew and differentiate into the three germ layers (ectoderm, endoderm, and mesoderm) and thus have the potential to play an important role in regenerative medicine and cell therapy. With cellular reprogramming via a cocktail of factors, it is possible to transform adult somatic cells into those of an embryonic state, i.e., iPSCs. A similar procedure can be used to reprogram somatic cells via factors present in the oocyte. Dr. Shinya Yamanaka shared the Nobel Prize for Medicine in 2012 for iPSC technology, and several research groups are actively pursuing this for diabetes treatment, regenerative medicine, and drug delivery, as well as for disease-modeling purposes. D. A. Melton's group at Harvard University demonstrated the preclinical development of glucose-responsive beta cells from human PSCs for the treatment of T1DM [70].

2.2.5 Mesenchymal stem cells (MSCs): Many research groups studying diabetes are using MSCs to generate insulin-producing cells 68, counteract autoimmunity [71,72], enhance islet engraftment and survival [73,74], and to treat diabetic ulcers and limb ischemia [75]. MSCs have also been shown to improve metabolic control in experimental models of type 2 diabetes [76]. In a preclinical study, A. O. Gaber, A. Grattoni, and colleagues differentiated human bone marrow-derived MSCs into islet-like insulin-producing cell aggregates and encapsulated them in a platelet lysate-based gel matrix housed in a 3D-printed polymeric device [38]. These cells remained viable and secreted insulin for several weeks, demonstrating the potential of this autologous transplantable system for treating diabetes. In another preclinical study by Kauer *et al.* [43], bone marrow-derived human MSCs and murine neural stem cells were encapsulated in a synthetic extracellular matrix and administered to the site of tumor removal in a mouse model of glioblastoma multiforme. With this method, there was a prolonged retention of encapsulated cells, tumor-targeted migration, and the release of therapeutics, resulting in reduced tumor sizes

and an increase in the survival rate. The success of this study indicates that a patient's own stem cells can be manipulated to deliver anticancer agents to improve survival.

2.2.6 Adipose-derived cells: Adipose-derived stem cells are easy to isolate, secrete several angiogenic factors, and have great promise for the regeneration of ischemic tissue. However, their survival after transplantation is poor. Cheng *et al.* [77] showed that this limitation can be minimized by sustaining their release via encapsulation in a thermosensitive chitosan/gelatin hydrogel. In another study, Xu *et al.* [78] used a high-density 3D micromass model system to improve early chondrogenesis with adipose-derived cells.

Adipose-derived regenerative cells are a blend of adult stem cells, endothelial progenitor cells, leucocytes, and smooth muscle cells. They can differentiate into several tissue types, such as bone, cartilage, fat, and skeletal, smooth, and cardiac muscles, and thus possess great promise for use regenerative medicine. Cytori Therapeutics, Inc., is conducting a safety and feasibility clinical trial (NCT01556022) to evaluate these regenerative cells derived from the patient's own adipose tissue and specifically formulated for the treatment of chronic myocardial ischemia.

2.2.7 Fibroblasts: Fibroblasts are also widely investigated for encapsulated transplantation. In an *in vitro* study, mouse NIH 3T3 fibroblasts encapsulated in calcium alginate remained viable for up to 150 days and released vascular endothelial growth factor for several weeks, suggesting that they may be able to induce angiogenesis and maintain cardiac function post-MI [79]. As a potential treatment for retinal dystrophies, microencapsulated fibroblasts that were genetically engineered to secrete human basic fibroblast growth factor were shown to survive for 90 days *in vitro* and upon xenogeneic transplantation in rats [80,81]. The encapsulation of genetically engineered fibroblasts is also being evaluated for treatment of spinal cord injury [82].

In the majority of cases, the encapsulation of transplanted cells improves their *in vivo* viability and intended therapeutic function by providing a protected environment. Different strategies, a variety of natural and synthetic materials, and their combinations have been investigated for this purpose, which are presented in section 3.

3. Strategies for Encapsulated Cell Transplantation in Diabetes

Based on the geometry of the encapsulation system, the encapsulation strategies can be classified as microencapsulation, wherein individual cells are enveloped in a micron-scale immunoisolating membrane, or macroencapsulation, wherein groups of cells are encased in a suitable membrane that could further be housed in a device. In this section, we describe the different types of microencapsulation materials, their clinical applications in diabetes treatment, the various macroencapsulation systems, and their clinical status in diabetes treatment, followed by the clinical advancements of encapsulated cell transplantation for treating various disease conditions, including chronic eye and neurodegenerative diseases, cancer, chronic wounds, cardiovascular diseases, and kidney dysfunction.

3.1 Encapsulation materials

Cell coating and microencapsulation are two strategies being explored extensively to address the immune rejection of transplanted cells. Whereas cell coating refers to the deposition of a suitable polymeric membrane onto the cell surface, microencapsulation involves the encasement of single cells or clusters in a polymeric matrix or membrane of a micron-range thickness. Both cell-coating and microencapsulating materials enable the immunoisolation of transplanted cells by preventing the entry of and interaction with host immune cells, antibodies, and complements several kilodaltons in size. Thus, they provide permselective protection to the encapsulated cells while allowing essential small molecules from the host to diffuse into the

graft and hormones, metabolites, and wastes to be released from the encapsulated cells. Although adverse effects have been associated with large volumes of the encapsulated grafts, the thickness of the capsule membrane influences the permeability for substance exchange and the diffusion rate of the therapeutic agents [35,83]. The size of the microcapsules influences the site of the transplant and the immunogenicity of the microcapsule system. The diffusive properties and mechanical stability of the microcapsules were significantly enhanced *in vitro* by reducing the capsule size from 1,000 μm to 400 μm, which improved the functioning of encapsulated rat islets and murine hepatocytes (Fig. 3) [84–86]. The first microcapsules were designed to be 600–800 μm in diameter, and now with conformal coating, it is possible to achieve close to 200-μm diameter capsules, rendering the system able to be implanted in retrievable sites within the body [87–89].

In addition to size, the biocompatible and biodegradable properties of the encapsulating material are vital to the design of the therapeutic system specific for the therapeutic application as well as for the success of the transplant. In the case of encapsulation devices that function as bioartifical organs, a biocompatible material will elicit no host immune response but favor the survival and function of the encapsulated cells. Purity, physiochemical and surface characteristics, and bulk properties such as permeability, diffusion and degradation rate of the material are factors that contribute to biocompatibility [90]. We can ascertain the biocompatibility of the encapsulating material upon transplantation can be ascertained by some common indicators such as the growth of pericapsular cells, viability and proliferation of the encapsulated cells, immune response of the host, inflammatory response at the site of implantation and the retrievability of the system and encapsulated cells [91,92]. We can ascertain the biocompatibility of the encapsulating material upon transplantation by some common indicators such as the growth of pericapsular cells, viability and proliferation of the encapsulated cells, immune response of the host, inflammatory response at the site of implantation and the retrievability of the system and encapsulated cells [93,94]. Furthermore, the encapsulating material may be required to be biodegradable or non-biodegradable based on the application. For example, for the purpose of tissue regeneration and wound healing, biodegradable and bioresorbable polymers are favored as it excludes the need for surgical resection of the system whereas for long-term treatment of diseases such as diabetes and anemia, materials with low degradation rates are essential [93,95]. Naturally occurring polysaccharide materials such as alginate, agarose and carrageenan are non-biodegradable while chitosan and hyaluronic acid are biodegradable [94]. However, by incorporating polymers or components that undergo hydrolysis or enzymatic degradation, the biodegradability of the materials can be altered [95]. Alginate is rendered biodegradable by oxidation, combination with fibrin or incorporation of metalloprotease cleavable sequences in its structure [96–100]. Overall, a large number of natural and synthetic materials are being developed and continuously tuned to achieve desired encapsulation properties. The American Society for Testing and Materials (ASTM) has established guidelines for the use of alginate and chitosan and the selection of suitable methods to evaluate their safety for tissue-engineered medical products (TEMPS) [101]. Likewise, the physical and chemical parameters of various other encapsulating materials such as purity, viscosity, molecular weight, endotoxin levels, monomer content and bioburden need to be standardized for their intended application in order to facilitate appropriate selection of material and ensure consistency and safety of encapsulation systems.

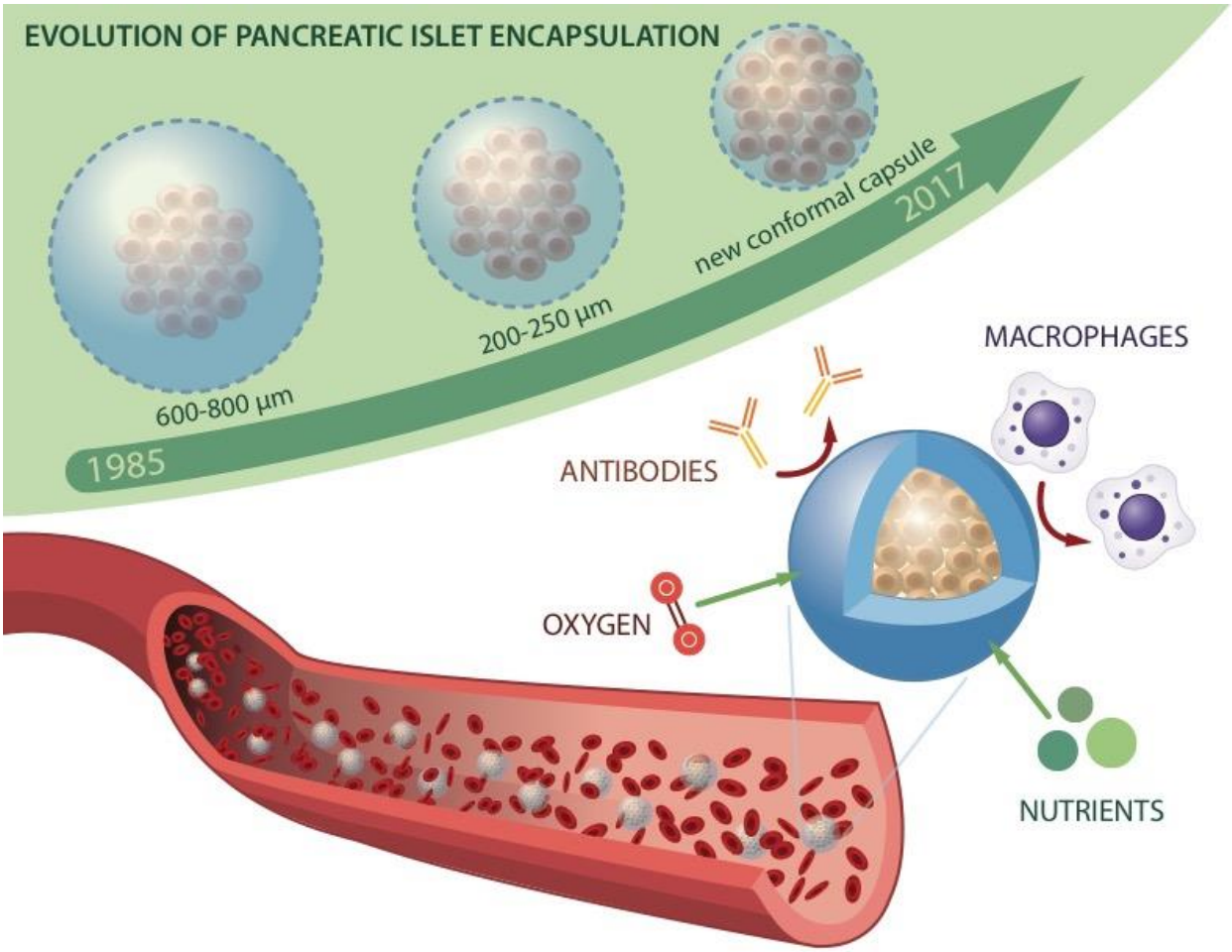

Figure 3: *Schematic of conformal coating and microencapsulation in pancreatic islet transplantation. Over the years, significant efforts were spent to minimize the ratio between the encapsulation volume and surface area. The semipermeable membrane protects the encapsulated cells from the immune system of the recipient, while permitting the diffusion of molecules such as nutrients, oxygen, glucose, and insulin.*

3.2 Microencapsulation Systems

Microencapsulation strategies utilizing different types of natural as well as synthetic materials are being evaluated based on the biochemical properties of the materials and the functional requirements of the transplanted cells. Here, we introduce the various microencapsulation techniques.

3.2.1. Alginate microcapsules

Alginate has been widely explored as an encapsulating material due to the ease of generating microspheres, its ability to rapidly cross-link and form gels, and the flexibility of incorporating other functional polymers and is extensively evaluated in several preclinical and clinical trials [28]. Alginate does not have significant permselectivity against immune cells and factors that can destroy the encapsulated cells [102]. As such, polycations, including poly-L-lysine [103], poly(vinylamine) [104], poly(allylamine) [105], poly-L-ornithine [23], and chitosan [106], have been used as coating materials in alginate microcapsules to optimize the porosity and enhance

the efficacy and the biocompatibility of the microcapsule system. A typical tri-layer alginate microcapsule comprises an alginate core surround by a semipermeable polycationic layer and an alginate outer shell. However, the host immune response remains one of the main factors leading to the necrosis of crude alginate-microencapsulated cells [107]. Derived from seaweeds and algae via harsh chemical regimens, in its crude state contains protein residues and toxins, including “pathogen-associated molecular patterns,” which trigger inflammation, cell protrusion, and the complete fibrosis of the microcapsules [107,108]. A high concentration of mannuronic acid in the alginate copolymer is also known to elicit fibrosis. The stability of the outer alginate layer is important, as it contributes to the masking of the inflammatory response by the poly-L-lysine layer. Microencapsulation of islets using highly purified alginate and crosslinking with multivalent cations such as barium has shown to protect the encapsulated graft from host immune attack and prolong islet survival by enhancing capsule stability and mechanical strength and by minimizing fibrosis [109]. Physical (surface roughness and charge) and mechanical (elasticity) properties of the alginate microcapsules also play roles in determining the survival of the encapsulated cells [110–112]. However, the optimal values of these parameters corresponding to the recipient and the site of transplantation are yet to be established from clinical studies.

3.2.2. Polyethylene glycol (PEG) coating

To overcome the *in vivo* cytotoxicity and the instability of poly-L-lysine and other polycations, PEG and various polymers (e.g., chitosan, xanthan, agarose, and cellulose) are used as coating materials [28]. The low immunogenic potential of PEG and its stability under physiological conditions, tunable biomechanical properties, controllable protein adsorption, thickness, and porosity make it highly suitable for cell microencapsulation [113,114]. PEG-based microencapsulation systems with a variety of shapes have been designed. When subjected to glucose challenges, PEG-encapsulated islets have been shown to release insulin and promote normoglycemia in immunocompromised diabetic mice for 110 days [115]. PEG-encapsulated islets were also clinically assessed [116] and are currently being evaluated as conformal coatings in combination with Matrigel in advanced preclinical studies. The main drawback of the PEG coating is that it creates an unfavorable cell microenvironment; however, this can be overcome by incorporating collagen and laminin [117].

3.2.3. Agarose microcapsules

Agarose exhibits several properties suitable for a microencapsulating material. As a responsive polymer, aqueous solutions of agarose undergo a sol–gel transition with changes in temperature [94,118]. Although the random coil conformation is maintained during this sol–gel transition, when cooled, it transforms to a double helix. At approximately 37°C, this transformation can be employed for encapsulating cells in agarose. As a naturally occurring polysaccharide obtained from red algae, agarose is less likely to trigger fibrosis or a host inflammatory response and is not biodegradable, which make it suitable for long-term implants [119].

3.2.4. Cellulose microcapsules

The Cell-in-a-Box® microencapsulation system, developed by PharmaCyte Biotech in partnership with Austrianova, utilizes cellulose sulfate and polymers such as polydiallydimethyl ammonium chloride to encapsulate genetically modified cells or beta cells by droplet formation. A combination of natural biocompatible and encapsulating polymers is passed through a microfluidic device to form microdroplets as a semipermeable membrane housing the therapeutic cells. The 0.7- to 0.8-mm-sized microdroplets housing insulin-producing cells, referred to as the artificial pancreas, are used for the treatment of T1DM and insulin-dependent type 2 diabetes. Preclinical studies showed that the transplantation of porcine insulin-producing

islet cells in diabetic rats restored normal blood glucose levels, which were maintained for 6 months [120]. Similar microdroplets encasing approximately 10,000 genetically modified liver cells, referred to as the artificial liver, activate the chemodrug ifosfamide at the site of a tumor, killing the tumor. A clinical trial of the artificial liver is being initiated for the treatment of locally advanced inoperable pancreatic cancer [121–126].

Although the various encapsulating materials demonstrate different advantages for immunoisolating the graft, there are several hurdles remaining before they are clinically deployed, beginning with the choice of a suitable site for transplantation. For example, subcutaneous transplantation is of interest as it is a minimally invasive procedure. Although subcutaneous tissue can provide sufficient oxygen tensions of 20 to 40 mmHg, there is no evidence that cells, such as pancreatic islets, transplanted into an unaltered subcutaneous site can reverse diabetes in humans or in animal models [127–130]. It is possible that the vascularization in subcutaneous tissue is inadequate, thereby presenting an inhospitable microenvironment and necessitating angiogenic stimulation to ensure successful islet transplantation. For this reason, oxygen generators [131], polymers [132,133], meshes [134], encapsulation devices [135,136], matrices [137], and growth factors such as fibroblast growth factor, vascular endothelial growth factor, and hepatocyte growth factor [137], as well as cotransplantation with MSCs, have all been explored with some success [138,139]. Another critical issue is the adverse tissue responses against the transplanted capsules. Some of the reactions may be linked to the encapsulation material or its components, such as the pathogen-associated molecular patterns, which strongly trigger inflammatory responses, present in alginate.

Another challenge associated with most encapsulation systems is cell protrusion [108]. Excessive protrusion is known to generate severe inflammatory responses that result in fibrosis of the transplanted microcapsules and necrosis of the transplanted cells. The different elasticities and the mechanical robustness of the capsules [115], which determine the optimal conditions for cell survival and functioning, are yet to be established. Along with these properties, factors such as roughness, the charge of the microcapsule surface [103,140] and the adsorption of protein [141,142] are vital to the success of the transplant.

One of the main limitations of all microencapsulation approaches is that the transplanted cells cannot be retrieved in the case of an adverse reaction. This represents a safety concern, particularly in the case of stem cells, which have unclear long-term fates and the potential to differentiate into tumors [143,144]. There is also no way to monitor the delivered encapsulated cells. Once the microcapsules are transplanted, the only way to assess their functional state is via invasive recovery surgery. However, Barnett *et al*. [145] have designed an interesting method to address this issue by using alginate-based radiopaque microcapsules, comprising barium sulfate or bismuth sulfate, which can be observed by X-ray. Although, the radiopaque agents did not affect cell viability or capsule permeability, the other materials employed in this work require more extensive examination.

3.3. Microencapsulation in Diabetes

In this section, we describe recent developments and the deployment of microencapsulation systems in the field of diabetes treatment. Table 1 shows the relevant microencapsulation materials, cell sources, and sites of implantation for these systems. Their applications in other disease treatments are discussed in section 4.

Table 1: *Clinical studies of microencapsulation systems for different application fields.*

Company - Institution	Material	Cell source	Graft site	Phase	Ref.
DRI	PEG-MG	Xeno-allo pancreatic islets	Epididymal fat pad	Preclinical	[140]
LCT	PLO-Alginate	Porcine Insulin cell	Peritoneal cavity	I/IIa	[144]
Encapsulife	Organic polymers	Xeno-allo pancreatic islets	Peritoneal cavity	Preclinical	[134-135]
Vicapsys	Alginate	Porcine islet cell graft	Intraperitoneal cavity	Preclinical	[145-146]

Agarose-encapsulated grafts were first shown to reverse diabetes in 1988 by Iwata *et al.* [146], where the nonobese diabetic mice with allografts survived for 80 days and those with isografts survived past the end of the study. In a more recent syngeneic islet transplant study without immunosuppression, agarose-microencapsulated islets were functional for more than 100 days after transplantation into mice [147]. The encapsulated islets survived autoimmune destruction whereas the nonencapsulated islet grafts lost their function within 2 weeks and were destroyed after complete infiltration of mononuclear cells.

The transplantation of alginate-microencapsulated human pancreatic islets was partially successful in a clinical study in 1994, resulting in limited survival post-transplantation [148]. Interestingly, alginate-microencapsulated neonatal porcine islets were functional and survived more than 9.5 years after they were implanted intraperitoneally (15,000 Islet equivalent (IEQ)/kg) in a T1DM patient in 1996 [149–151]. In addition to the 30% insulin reduction, there were no signs of xenosis or fibrosis of the graft.

Encapsulife designed an interesting approach to eliminate the need for immunosuppressive drugs and to achieve immunoisolation of the transplanted pancreatic beta cells. In this approach, islet cells microencapsulated in a five-component triple-layered polymeric system were simply anchored without attachment to the peritoneal cavity during a 15-min laparoscopic procedure. This method of implantation enabled optimal nutrient and fluid exchange for the transplanted islets and stimulated insulin production. When canine pancreatic islets encapsulated via this approach were transplanted into the peritoneal cavities of pancreatectomized canines, the fasting blood glucose levels of all nine experimental subjects were normalized for 214 days without the use of immunosuppressive or anti-inflammatory drugs [152,153].

Alginate-encapsulated beta cell grafts were tested along with systemic immunosuppression via basiliximab, anti-thymocyte globulin, tacrolimus, or sirolimus by a group led by B. Keymeulen at AZ-VUB and the University Hospital Brussels, Belgium, demonstrating a better outcome than with nonencapsulated controls in an immunodeficient mouse model [154,155]. An ongoing phase II clinical trial, NCT01379729, is assessing the graft survival and function of allografts of microencapsulated beta cells implanted in the peritoneal cavities of nonuremic T1DM patients. These microencapsulated grafts produced glucose secretory responses in both mouse and human studies. Dr. Riccardo Calafiore and his team at the University of Perugia, Italy, are developing microcapsules of human islets in a sodium alginate and poly-L-ornithine microbead-based system [156,157]. Clinical evaluations in nonimmunosuppressed T1DM patients have shown that no immune responses are elicited by the intraperitoneally transplanted

microcapsules, even after subsequent implants. However, the metabolic efficacy was limited due to poor oxygen and nutrient supply, affecting insulin secretion [89].

Islets are not uniform in size, ranging from 50 to 350 μm. By contrast, typical microcapsules are uniform, ranging in size from 500 to 1,500 μm. Thus, larger volumes for grafts of encapsulated cells can result in islet aggregation and poor oxygen and nutrient distribution, potentially leading to necrosis. Microencapsulation methods involving a thin coating to maintain volumes comparable to those of the naked islet grafts are being assessed to address this [111]. A. Tomei and her team at the Diabetes Research Institute of Miami are developing a system in which islets are conformally coated (shrink wrapped) with a PEG hydrogel layer and Matrigel extracellular matrix [158]. This system is characterized by enhanced immunoisolation and islet function due to its permselectivity and minimal immunogenicity [158]. The aim of this process is to facilitate implantation at favorable sites and to minimize core hypoxia and delayed insulin release [88]. This method did not negatively affect islet function *in vitro* or *in vivo* [159]. When conformally coated PEG-Matrigel islets from BALB/c mice were transplanted into the epididymal fat sites of diabetic C57BL/6 mice at a dose of 750–1,000 IEQ/mouse, the islets survived for more than 100 days without the administration of immunosuppressive drugs [158].

Another trilayered encapsulation technology of significance is IMMUPEL™, developed by a New Zealand-based company, Living Cell Technologies, Ltd. DIABECELL™ and NTCELL® both utilize the IMMUPEL™ technology—in which a poly-L-ornithine layer is sandwiched between alginate layers—eliminating the need for immunosuppressive regimens post transplantation [143,160]. Xenogeneic transplants of DIABECELL® lower the daily insulin requirement in diabetic rats and in NHPs [161] and show favorable safety profiles in mice, rabbits, and dogs. In human trials conducted in Argentina, New Zealand, and Russia, DIABECELL® was safely implanted in the peritoneal cavities of T1DM patients. Hemoglobin A1c levels, insulin doses, and unaware hypoglycemic events were significantly lowered with increased dosage [162]. With no signs of adverse reactions after up to 3 implants per patient, 6 patients demonstrating long-term blood glucose control, and the remaining 2 patients showing complete insulin independence for up to 8 months, DIABECELL® was clinically approved in Russia in 2010.

The VICAPSYN™-eluting alginate system is an advanced microencapsulation technology from VICAPSYS aimed at encapsulating and protecting the islet graft. This 200–600-μm system is designed to comprise 1–2 human or porcine islets microencapsulated by biocompatible polymers that gradually release VICAPSYN™, which provides immunoisolation by repelling T cells and prevents fibrosis and graft rejection. The angiogenic properties of VICAPSYN™ are proposed to enhance the perfusion of the islets and enhance vascularization at the transplant site. No inflammatory cells were observed after CXCL12-incorporating alginate microcapsules were transplanted adjacent to the mesentery in the intraperitoneal cavities of healthy NHPs, whereas capsules devoid of CXCL12 were marked by significant inflammation and fibrosis [163]. Two autologous transplants of the encapsulated islets were found to be functional when retrieved 30 days post-transplant. Allogeneic islet transplant studies are ongoing [163,164].

In a recent study in streptozotocin-induced diabetic mouse model, intraperitoneal transplantation of coencapsulated human islets and human mesenchymal stem cells in calcium alginate - PEG crosslinked microcapsules, showed that mesenchymal stem cells interact with N-cadherin and enhance islet insulin secretion. The mesenchymal stem cells also provided a stromal structure for the islets and supported prolonged viability and functioning of the islets [165].

3.4. Macroencapsulation systems

Microencapsulation and cell-coating strategies have achieved important milestones, particularly, in limiting the host immune system's access to the transplanted cells [47]. However, maintaining cell survival is still a major challenge for the many reasons previously described, including dispersion, suboptimal oxygenation, and engraftment [166,167]. To overcome these challenges, macroencapsulation systems comprising larger devices with a planar or cylindrical geometry have been developed to provide a suitable microenvironment for the cells. The reservoirs of these implantable devices are often designed to prevent cell clustering while protecting the cells from mechanical stress. Importantly, the permeable flat sheet membranes or the lumens of semipermeable hollow fibers prevent direct contact between the cells and the host tissues. An additional significant advantage of macroencapsulation is that it provides the ability to retrieve the cells in the case of loss of function, adverse effects, or malignant transformation [168,169].

Macrocapsules are classified into two main categories: i) intravascular systems, which connect the graft as a shunt to the systemic circulation, and ii) extravascular devices, which rely on of new blood vessel formation at the host tissue–device interface [111,166,170]. In some intravascular devices, the cells are encapsulated within a semipermeable membrane containing polymeric capillaries. After transplantation, these devices are connected directly to the recipient's systemic circulation by vascular anastomoses, creating an intravascular shunt. The close proximity to the blood stream constitutes an important advantage in terms of ideal oxygen and nutrient supply, thereby enhancing graft survival [166]. This feature is also of paramount importance with regard to cells whose therapeutic function is to secrete molecules in real time in response to biological stimuli, as is the case for pancreatic islets. However, intravascular systems also generate a risk for thromboembolic events, which require intense anticoagulation therapy and are associated with adverse effects (e.g., bleeding and gangrene). Because of this, intravascular devices are not suitable for routine clinical application. By contrast, extravascular devices are typically associated with a lower risk to the recipient. These systems are designed as either tubular or planar diffusion chambers that can be implanted in the peritoneal cavity, an omental pocket, or subcutaneous tissues, making the procedure simpler and less invasive while eliminating most major surgical complications.

Despite the advances in cell engineering, it is unlikely that transplanted cells will survive and function indefinitely. Therefore, the clinical deployment of these systems should entail strategies for substituting or replenishing cells. To this end, extravascular macroencapsulation devices, especially those designed for subcutaneous implantation, are retrievable and enable transcutaneous cell loading and replacement.

Diabetes is a medical field for which macroencapsulation strategies have been most widely explored for decades. In the sections 3.4.1 and 3.4.2, we present early developments involving the use of macroencapsulation devices in diabetes, followed by current approaches in advanced preclinical and clinical studies.

3.4.1. Early macroencapsulation strategies in diabetes

One of the pioneering studies for implanting insulinoma tissues in a permselective membrane was by Dr. Bisceglie in 1933, which focused on determining how the absence of vasculature affected the survival of implanted tissues. The extravascular diffusion device based on a flat membrane system was first developed by Dr. Algire and his colleagues Drs. Prehn and Weaver. They studied the cellular mechanisms of both tissue rejection and tumor growth, the results of which were reported in a series of publications from 1948 to 1959 [166–174]. Notably, they found that although allograft survival was achieved by host cell exclusion, it was not sufficient to protect xenograft transplants long term. This work led to the strategy of artificially creating an

immune-privileged site for cell implantation and opened the door for the pancreatic islet encapsulation studies that followed.

In the 1970s, Millipore Corporation produced extravascular transplantation chambers for allotransplants in accordance with Algire's approach. These devices featured membranes with pore sizes on the order of 450 nm, with the objective of preventing direct cell–cell contact between the graft and the host [175]. *In vivo* assessments showed that the cells remained viable for only a few weeks. Fibroblast overgrowth around the device was observed, which raised concerns about device biocompatibility. To reduce this fibroblastic response, attempts were made to coat the outer surfaces of the membranes with collagenase [176]. This approach eliminated the fibrous capsule that was directly in contact with the membrane. However, a fibrotic encapsulation still formed at a short distance from the membrane, which limited the inward and outward diffusion of molecules and nutrients [177].

Additional factors challenging the success of these permselective systems were ascribed to the lack of mechanical robustness and the chemical stability of membranes *in vivo*. However, new approaches for encapsulation were fostered by the development of silicon nanofluidic systems based on microfabrication and sacrificial layer techniques [178]. In fact, the peculiar properties of transport within nanochannels [179,180] could be leveraged to achieve better control of molecule permeation and diffusion via physical and electrostatic confinement [181–183]. Beginning in the early 1990s, M. Ferrari, T. A. Desai, and colleagues microfabricated capsules with regular patterns of slit-nanochannels in sizes smaller than 100 nm [184] for molecular sieving [185] and cell immune isolation [186,187]. They showed that islets and insulinoma cells encapsulated in these systems within a supportive matrix were viable and glucose responsive *in vitro* and *in vivo* in mouse models [188]. These silicon-based systems provided enhanced mechanical robustness and biocompatibility [189], resulting in minimal fibrotic encapsulation around the device. However, long-term graft survival was still an issue, likely due to the lack of proper cell oxygenation.

In the late 1990s, Baxter Healthcare, which subsequently became Theracyte™, provided an important contribution in the field of macroencapsulation systems by designing a double-membrane planar device to address vascularization and immune protection [190]. An outer Teflon membrane provided mechanical strength and promoted capillary ingrowth, while an inner hydrogel semipermeable membrane was used to protect the allograft from immune responses. A high level of subcutaneous vascularization was achieved in rats and cell function was shown [133,191]. Despite these promising results, fibrotic capsule overgrowth hindered cell retrieval. Nevertheless, Baxter's technology is still used by various research groups and important players in the cell encapsulation field, such as Living Cell Technologies, Ltd., Betalogics of Janssen Pharmaceuticals, and ViaCyte, Inc. (San Diego, CA).

Other macroencapsulation strategies using alginate were developed in the late 1990s to achieve immune protection and to support cell viability and function. Encapsulated islets implanted by Suzuki *et al.* into the epididymal fat pads of streptozotocin-treated diabetic mice retained *in vivo* viability and function for 12 weeks [192]. Islet Sheet Medical developed alginate-based islet sheets (250 μm) and tested them with allogenic islets sutured onto the omenta of dogs, which demonstrated normoglycemia for 84 days [193]. More recently, human islets were encapsulated within the islet sheets and survived both *in vitro* and *in vivo* in rats [194].

A number of approaches have recently been developed by various other companies, but they have not been clinically evaluated. These include the encapsulation of porcine islets in a hydrogel matrix supported by a polyester net developed by Encelle, Inc., for intramuscular

transplantation and a flexible tube designed by BetaGene in partnership with Gore Hybrid Technologies for the subcutaneous implantation of islets.

3.4.2. Current macroencapsulation strategies in diabetes

More recently, external oxygen supplementation, vascularization of the devices prior to cell transplantation, and the use of autologous cell sources have been adopted as strategies to attain long-term cell survival. Despite the difficulties in achieving suitable vascularization, subcutaneous implantation is now considered a target approach. The advantages include the reduced invasiveness of the surgical procedure and the potential for the transcutaneous loading, replenishment, and retrieval of cells. Table 2 lists recent macroencapsulation technologies that are under advanced preclinical and clinical investigations, which are discussed in greater detail below.

Table 2: *Macroencapsulation systems currently under advanced stages of development for diabetes treatment.*

Company - Institution	Material	Cell source	Graft site	Phase	Ref.
TheraCyte	PTFE membrane	Islet ESC-derived	Subcutaneous	I	[171]
Beta-O_2 Technologies	Teflon/Alginate	Human pancreatic islets	Subcutaneous	I/II	[178]
ViaCyte	PTFE membrane	Human embryonic stem cells	Subcutaneous	I/II	[180-182]
Houston Methodist Hospital	Medical grade polymer/Silicon	Human pancreatic islets/beta cells	Subcutaneous	Preclinical	[35,36]
Monolayer Cellular Device	Alginate	Pig islets	Subcutaneous	I	[197]
Defymed	Medical-grade polymers	Insulin-secreting cell	Subcutaneous	Preclinical	[192]
DRI	Plasma-thrombin biologic scaffold	Human islets	Omentum	I/II	[202]
Sernova	Medical grade polymers	Human Islets	Subcutaneous	I/II	[191]

βAir: To improve cell oxygenation within the device, an implantable bioreactor was developed by the Israel-based company Beta-O_2 Technologies Ltd. This device, named βAir (Fig. 4A), is a subcutaneous system comprising a reservoir containing islets encapsulated in an alginate hydrogel slab and a gas chamber that enables oxygen supplementation through a tubing system. The oxygen from the gas reservoir passes through a silicon membrane, whereas a porous membrane protects the islets from immune rejection. Preliminary studies in rats and pigs showed that daily oxygen supplementation preserved islet function for up to 90 days [195]. In 2012, βAir was implanted in a 63-year-old patient in Germany. The case report indicated that the islets retained their function for the 10-month study duration, achieving persistent graft function, regulated insulin secretion, and preservation of islet morphology and function without immunosuppressive therapy [196]. Recently, a phase I/II clinical trial was completed (NCT02064309) [197] in four T1DM patients to investigate the safety of the implanted βAir device containing human islets but also to evaluate its efficacy in improving glycemic control and to determine the incidence of hypoglycemic episodes. In this trial, 1800-4600 islet

equivalents per kg body weight were encapsulated in βAir devices. At the end of 3-6 months study, devices were proved safe and successfully prevented immunization and rejection of the transplanted tissue (Fig. 4B) [196]. However, C-peptide levels detected in the blood stream were limited. Other key developments proposed by Beta-O_2 Technologies are a market-ready version-2 device that holds a sufficient amount of beta cells to replace insulin altogether rather than as an add-on to insulin therapy and an advancement from cadaver cells to stem cells in the coming years.

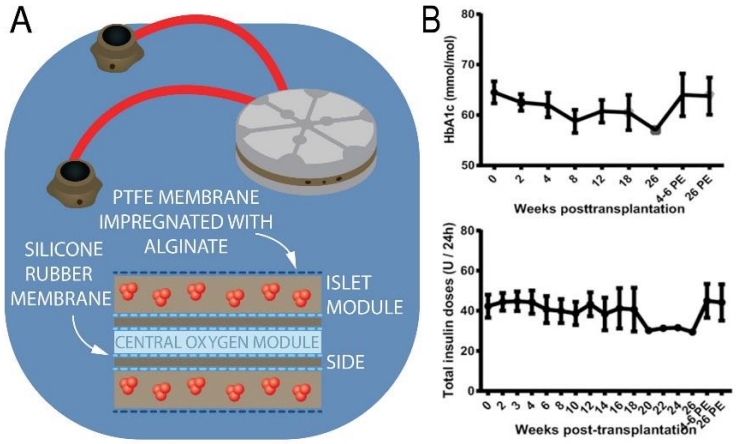

Figure 4. *(A) Schematic of the βAir device showing the central gas module connected to the two access ports for exogenous oxygen refueling. The core of the device can be charged with oxygen to diffuse outwards to the two compartments surround the central gas cavity where alginate-immobilized pancreatic islets are housed. The central module is covered by hydrophilized PTFE porous membranes. (B) means ± standard error of the mean (SEM) of HbA1c and total insulin doses for the 4 patients; 4- 6 PE and 26 PE indicate the follow-up, meaning 4- 6 and 26 weeks postexplantation, respectively.*

PEC-Encap™ and PEC-Direct™: Over the past decade, ViaCyte, Inc. developed two subcutaneously implantable devices to encapsulate stem cell-derived pancreatic progenitor cells (PEC-01™) for diabetes treatment. Both devices promote vascularization prior to cell transplantation to avoid graft hypoxia events [112]. The PEC-Encap™ device (Fig. 5) has an immunoprotective membrane (Encaptra®) that allows oxygen and nutrients to permeate from the vasculature while limiting the access of immune cells. By contrast, the PEC-Direct™ device has a polymeric membrane that allows direct vascularization of the encapsulated cells within the deviceold. In this case, immunosuppressive regimens are required to protect the graft from immunorejection by the host. The PEC-Encap™ device was shown to retain robust graft function for at least 6 months after transplantation. In late 2014, ViaCyte began a phase I/II clinical trial (NCT02239354) [198] to test the safety and efficacy of subcutaneously implanted PEC-Encap™ devices over two years in T1DM patients. A 3-year follow-up safety study (NCT02939118) [199] was begun in 2016 involving subjects previously implanted with the PEC-Encap™ device; the expected recruitment is 200 patients. An open-label clinical trial is ongoing to evaluate the safety and efficacy of the PEC-Direct™ device (NCT03162926) [197]. The first implantation was announced by ViaCyte on August 1, 2017, which involved a collaboration between the University of Alberta Hospital in Edmonton, Alberta, and the UC San Diego Altman Clinical Trials Research Institute. The first cohort of T1DM patients were implanted with devices loaded with specific cells called sentinels, which will be examined histologically after the implants are retrieved to evaluate their engraftment and maturation. A second cohort of up to 40

patients will be used to evaluate the ability of the PEC-Direct™ device to release a clinically relevant level of insulin [200]; the first patient was implanted with a potentially efficacious dose of PEC-01™ cells on January 5, 2018. In the coming months, the company proposes to expand the trial to additional centers in Canada and the United States, including the University of Minnesota. Efficacy results from this trial are expected by the first half of 2019.

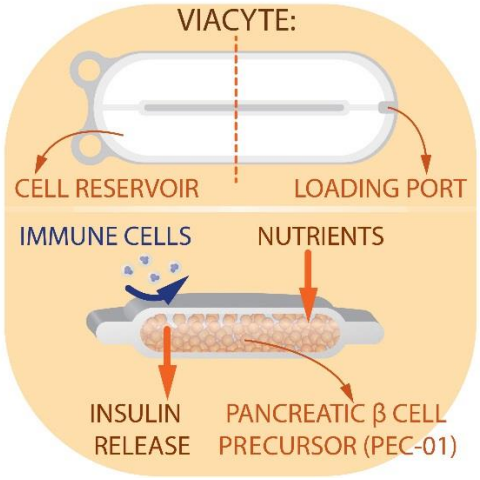

Figure 5. *Schematic of the PEC-Encap™ device, which is comprises an immunoprotective membrane (Encaptra®) that allows the transport of nutrients from the exterior of the device and hormones from the encapsulated cells.*

NICHE: To achieve an extensive vascularized environment prior to cell transplantation while avoiding graft rejection, our team at Houston Methodist Research Institute (Houston, TX) has developed two 3D-printed subcutaneously implantable architectures for the encapsulation of human pancreatic islets and beta cells obtained from different sources. The first system, named NICHE-1 (Fig. 6A), is for the transplantation of autologous insulin-producing cells and allows blood vessels to directly contact the cells within the device [37,38]. The second version, named NICHE-2, is designed for heterologous cell transplantation (Fig. 6B). It consists of a reservoir that houses cells in a fully prevascularized environment and a drug reservoir for the sustained release of immunosuppressive drugs *in situ* through a nanofluidic silicon membrane. Both systems include microwells that promote a homogeneous distribution of cells within the device while avoiding clustering. Furthermore, they allow blood vessels to penetrate while preventing the loss and dispersion of transplanted cells, as well as facilitate transcutaneous cell loading, easy retrieval, and the addition or replenishment of cells as needed [37,38]. To avoid hypoxic stress, the device is first implanted to allow for vascularization prior to the loading of cells. In the case of NICHE-2, sustained drug release through a nanochannel silicon membrane, which had been validated in several studies [181–183,185,187,201–203,203–206], is under investigation with immunosuppressants. The objective is to abrogate graft rejection by achieving an effective local concentration of immunosuppressants while minimizing systemic drug exposure and the associated adverse effects. Importantly, the system allows for transcutaneous drug replenishment for up to years once the drug reservoir is depleted without requiring the substitution of the implant. In a cocktail with immune suppression, the membrane could be used for a local sustained delivery of growth factors, nutrients, or oxygen to support the transplanted cells. The 3D-printing technology enables the NICHE design to be easily customized in accordance with the characteristics of the implantation site and the needed volume of transplanted cells. Although studies have been completed in rodents [37,38], the assessment of

vascularization and cell viability and function are under investigation in porcine and NHP models.

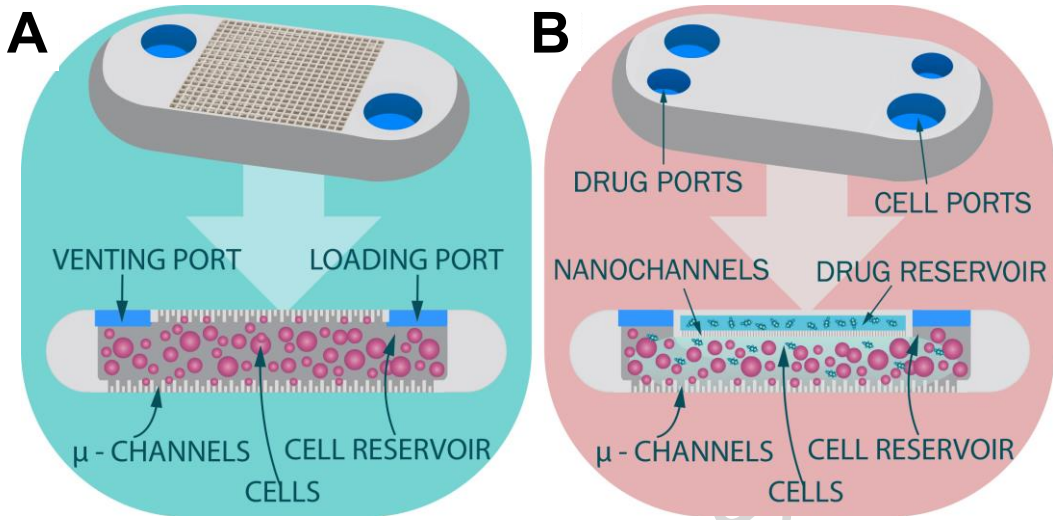

Figure 6. *(A) The NICHE-1 encapsulation system consists of a reservoir that houses autologous insulin-producing cells in a prevascularized environment. (B) Schematic of NICHE-2 composed of a fully vascularized cell reservoir for heterologous cells and a drug reservoir for the sustained release of immunosuppressive drugs in situ through a nanofluidic silicon membrane.*

Cell Pouch™: A different approach was developed by Sernova Corporation (Canada) [207] to enable the vascularization of a subcutaneous site before the cells are administered through a port. The discoidal device, named Cell Pouch™ (Fig. 7A), is implanted and maintained subcutaneously for 4 to 5 weeks before the islets are injected. After transplantation, these cells were proven to be functional, enabling diabetes reversal in a murine model (Fig.7 B,C) [207,208]. Sernova Corporation's islet cell replacement therapy for T1DM is currently in phase I/II development at the University of Alberta [209]. As the Cell Pouch™ device does not protect the transplanted cells from immune rejection, immunosuppressant drug administration is required. Additionally, Sernova developed the Sertolin™ technology to protect the injected insulin-producing islets from immune system attack. Preclinical studies are ongoing.

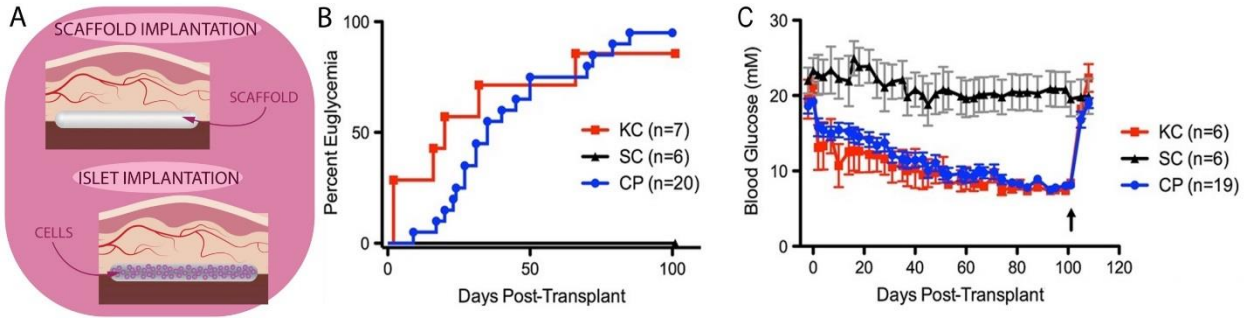

Figure 7. *(A) Cell Pouch™ system, where a polymeric scaffold is subcutaneously implanted and then removed, leaving a vascularized space where the islets are transplanted. (B) Reversal of diabetes rates, percent euglycemia, between islet-KC recipients (KC, n = 7) and mini-CP (blue, n = 20) recipients were comparable 100 days after transplantation. (C) Nonfasting blood glucose measurements of euglycemic recipients after transplantation. Recipient of marginal*

islet-KC and CP transplants maintained robust glycemic control until the time of graft retrieval (black arrow).

MailPan®: Defymed [210], a spin-off of the European Center for Diabetes Studies, is developing an implantable device known as MailPan® (macroencapsulation of pancreatic Islets) (Fig. 8), which is made from a nonbiodegradable biocompatible material and is primarily for T1DM applications but may also be used for several other diseases. MailPan® is a semipermeable device that is implanted into a patient's abdomen and is aimed to work as a bioartificial pancreas. Similar to other systems, MailPan® encapsulates insulin-secreting cells within the cell chamber made of membranes impermeable to the immune system but permeable to oxygen, nutrients, glucose, and insulin. Input and output ports enable cells within the device to be replaced without the need for surgery. In 2016, Defymed signed a strategic collaboration with Semma Therapeutics to use the MailPan® technology to encapsulate Semma stem cell-derived insulin-secreting cells. Pre-clinical studies are ongoing.

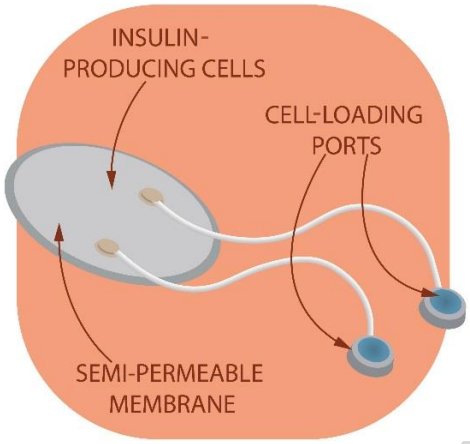

Figure 8. *Graphic representation of the MailPan® system composed of a cell chamber and two ports for external cell loading.*

In the macrodevices described above, the transplanted cells are housed between flat-sheet double membranes made with water-insoluble polymers [211], such as polytetrafluoroethylene (PTFE), polylactic acid, and Teflon. Other research groups adopt a "monolayer" configuration, where the cells are seeded as a monolayer within water-soluble polymers, such as an acellular collagen matrix and hyaluronic acid, to provide a more natural and potentially less immunogenic environment to the encapsulated cells [212].

Monolayer cellular device: The monolayer cellular device developed by Dufrane *et al*. [213] at the University Clinical Hospital Saint-Luc, Brussels, consists of a planar flat sheet of an acellular collagen matrix seeded with alginate-encapsulated porcine islet macrocapsules [214] (Fig. 9). Designated for subcutaneous implantation, it successfully controlled diabetes in cynomolgus macaques for 6 months, without the need for immunosuppression [212]. After new monolayer cellular devices were transplanted, their diabetes was controlled for up to 1 year. A monolayer cellular device was implanted in a 74-year-old T1DM patient, who showed no inflammation and no immunization against the donor cells for 361 days [215]. The graft was functional and his diabetes was controlled for 11 months after the transplantation, along with a 61% reduction in hypoglycemic episodes. The device was easily removed after 11 months, revealing the macroscopical integrity of the graft without signs of inflammation. In 2016, a phase I clinical trial involving 15 T1DM patients was completed at the Université Catholique de Louvain

(NCT00790257) [216]. In an NHP model, adult pig islets were cotransplanted with either bone marrow MSCs or adipose MSCs [217]. However, the MSCs only slightly improved the long-term function of the device, despite the improved oxygenation and neoangiogenesis [217].

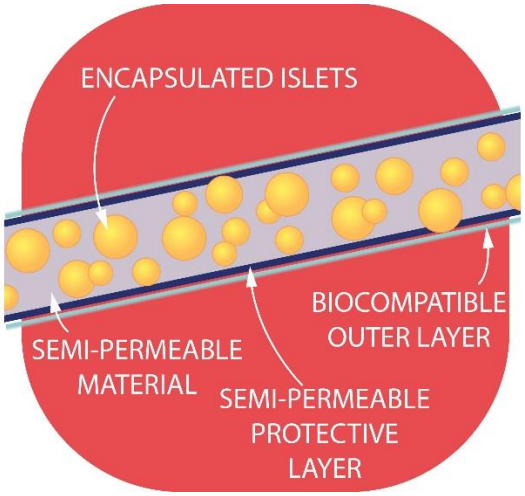

Figure 9: *Scheme of the planar monolayer cellular device consisting of a flat sheet made of acellular collagen matrix containing porcine islets encapsulated as alginate macrocapsules*

BioHub: Another technology for encapsulating pancreatic islets within a biological material was developed at the Diabetes Research Institute of Miami [218]. This scaffold system, known as BioHub, is composed of a gel-like substance made with thrombin and the patient's own plasma. The scaffold containing the pancreatic islets is then implanted on the patient's omentum (Fig. 10A). The gel degrades over time, leaving the islets intact, while new blood vessels are formed to support their survival and function. The omentum was chosen for its relatively easy access and dense vasculature. Studies conducted in small animal models demonstrated an improved metabolic function and cytoarchitectural preservation of the encapsulated cells within the highly vascularized BioHub scaffold, resulting in long-term nonfasting normoglycemia and adequate glucose levels [219]. BioHub is being evaluated in an ongoing clinical trial (NCT02213003) [220], for which some of the results were published in May 2017 by Baidal *et al.* [221]. They report that a 43-year-old woman with a 25-year history of TIDM, who received 602,395 islet equivalents from one deceased donor encapsulated within the BioHub scaffold, experienced restored normoglycemia and insulin independence for 12 months (Fig. 10B). Although this strategy requires the administration of immunosuppressive regimens, it demonstrates that the omentum is a good site for islet transplantation with the BioHub technique. The safety and long-term feasibility of this approach for islet transplantation will be determined in the ongoing study.

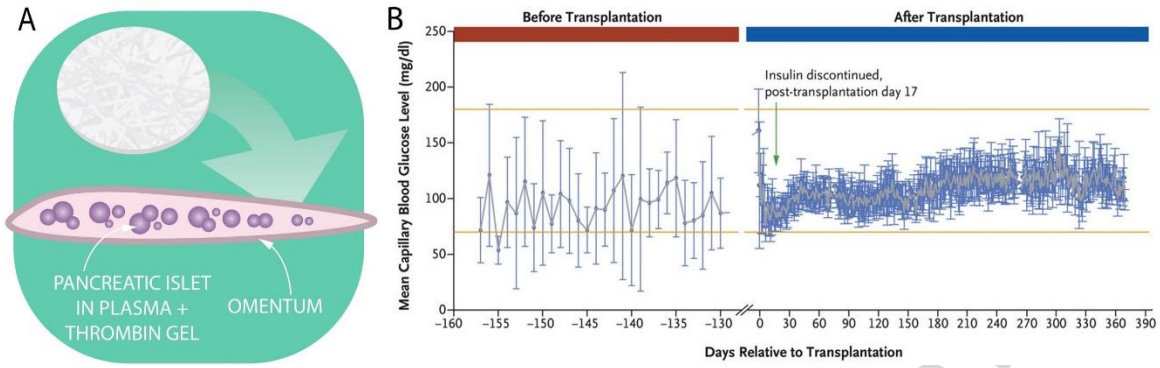

Figure 10. *(A) BioHub technology where the donor islet cells are combined within a biodegradable scaffold made with the patient's own plasma, thrombin, and a clinical-grade enzyme. The area of the omentum is then folded over around the scaffold. (B) comparison of 2012 capillary blood glucose values before and after transplantation. Upper and lower orange lines show the glucose range of 70 to 180 mg per deciliter.*

A more recent attempt to address the immune response and long term efficacy of invasive procedures of islet transplantation is the noninvasive microneedle patch-based system. The microneedle patch comprises of cross-linked hyaluronic acid housing pancreatic beta-cells and nano-vesicles containing glucose signal amplifying enzymes. In a hyperglycemic condition, glucose is expected stimulate insulin production by passing through the patch and interacting with the encapsulated beta-cells. Enzyme-based glucose signal amplifiers are designed to aid in stimulating insulin production. In streptozotocin-induced type-1 diabetic mice, a microneedle patch of about 10^7 beta cells lead to rapid stabilization of blood glucose levels for more than 10 h. Further work is required for improving the diffusivity of the patch material and optimizing the density and viability of encapsulated cells [222,223]. Another cell encapsulation system featuring easy retrievability and replaceability by means of minimally invasive laparoscopic procedure is the thread-reinforced alginate fiber for islets encapsulation (TRAFFIC) device. This device comprises of a calcium-releasing central polymeric thread with nanoporous surface attached to an alginate layer with controllable thickness for islet cell encapsulation. In vivo studies in C57BL/6 mice showed that the device was capable of providing immune protection relative to the thickness of the alginate layer for up to 7 months. TRAFFIC encapsulating rat islets restored normal blood glucose levels in C57BL/6 diabetic mice for 3 months while TRAFFIC encapsulating human islets showed diabetes correction in immunodeficient SCID-Beige mice for 4 months. Similarly, device scalability and retrievability was also demonstrated in dogs [224].

4. Cell Transplantation Beyond Diabetes

Many other medical conditions have been targeted with cell therapies and encapsulation strategies, especially those involving a protein deficiency (Table 3). Here, we present the most successful micro- or macroencapsulation approaches and applications that are already approved for clinical use or are currently under investigation.

Table 3: *Clinical studies of macroencapsulation systems for different application fields.*

Application	Company - Institution	Material	Cell source	Graft site	Phase	Ref.
Chronic eye disease	Neurotech	Implantable polymer	Human retinal pigment epithelial cells	Eye	II/III	[210]
Neurodegenerative diseases	NsGene	Implantable polymer	GDNF secreting cells	Intracranical	II	[230,231]
Neurodegenerative diseases	NsGene	Implantable polymer	NGF secreting cells	Intracranical	I	[237,238]
Cancer	MaxiVax	Implantable polymer	GM-CSF secreting cells	Subcutaneous	II	[246]
Wound healing	Organogenesis	Extracellular matrix	Fibroblasts/epidermal keratinocytes	Cutaneous	FDA approved	[254]
Wound healing	Organogenesis	Polyglactin scaffold	Fibroblasts	Cutaneous	FDA approved	[255,256]
Kidney failure	CytoPherx	Polycarbonate/ EPDM/niobium coated carbon	Renal epithelial cells	External	IIb	[265,265]
Kidney failure	Sentien Biotechnologies	Biocompatible polymers	Mesenchymal stem cell	External	I/II	[266,267]
Kidney failure	UCSF	Silicon	Human kidney tubule cells	Abdomen	Preclinical	[268-270]

4.1. Chronic eye diseases

Stem cell therapies are under development for several ophthalmic conditions, including age-related macular degeneration and diabetic retinopathy, as well as to provide trophic factors to protect compromised retinal neurons and to restore neural circuits. Neurotech Pharmaceuticals, Inc. (Cumberland, RI) [225] developed intraocular implants that deliver therapeutic proteins directly to the back of the eye for up to two years to treat a broad array of eye diseases. These implants contain human retinal pigment epithelium cells (NTC-201) engineered to produce and release therapeutic agents that are encapsulated in a semipermeable hollow-fiber membrane and protected by a permeable exterior capsule (Fig. 8A). The implant, termed Renexus® (NT-501), is surgically inserted in the vitreous and allows oxygen and nutrients to freely diffuse into the device and therapeutic agents to freely diffuse outward [226] (Fig. 11A). Phase II and III clinical trials are underway testing this polymeric device with NCT-201 cells secreting ciliary neurotrophic factor for the potential treatments of retinitis pigmentosa [227,228] and age-related macular degeneration [229], as well as for glaucoma neuroprotection 209 and vision restoration [230]. In June 2017, Neurotech announced the results of the phase II trial on macular telangiectasia (NCT03071965), showing a significant reduction in the progressive loss of photoreceptors at 24 months compared to that in untreated individuals [231]. This therapy has the potential to become the first treatment available for macular telangiectasia, with a phase III trial for the therapy planned to begin at the end of 2017. Neurotech is currently developing more advanced versions of this platform to improve its efficacy and reduce the scarring of the retina, as well as to treat wet age-related macular degeneration using devices secreting antagonists against vascular endothelial growth factor (NT-503) [232] and platelet-derived growth factor (NT-506).

4.2. Neurodegenerative diseases

Chronic degenerative central nervous system (CNS) diseases are currently the fourth leading cause of death, affecting over 37 million people worldwide [233]. Despite extensive research efforts, most of these diseases lack a cure. To date, the most promising approaches for their management involve the delivery of neurotrophic or angiogenic factors from engineered cells to slow, or even reverse, the ongoing degeneration and related neurological deficits [234,235]. Encapsulated cell therapy is a means to overcome the challenges of sustained controlled delivery of these factors across the blood brain barrier [236]. Moreover, early studies using xenografts in guinea pigs or NHP brains showed that cells in intact capsules remained viable, whereas unencapsulated cells were rapidly rejected [237,238]. Macrodevices encapsulating cells in semipermeable hollow-fiber membranes have been investigated for CNS pathologies such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease 152, 217-219.

PD is characterized by progressive and debilitating motor impairments due to the dysfunction of dopamine-secreting neurons in the substantia nigra. The use of cell therapy for PD was initially demonstrated by the implantation of encapsulated PC12 cells into the striata of rodents and NHPs [238,239]. Other studies demonstrated the benefits of glial cell line-derived neurotrophic factor (GDNF) for preventing nigral neuron loss and abnormal motor function and enhancing dopaminergic function [240,241]. However, GDNF cannot be effectively delivered to the brain via systemic administration. To overcome this, encapsulated cells that release approximately 5 ng GDNF/day were implanted immediately rostral to the substantia nigra in a small animal model. This method attenuated the loss of neurons without significantly affecting dopamine levels within the striatum [242–244]. Nevertheless, the levels of GDNF, or the related protein neurturin, delivered were not sufficient to produce clinically beneficial effects. Thus, new technologies to increase the levels of GDNF released are under investigation. NsGene A/S (Ballerup, Denmark) has developed a tubular device (Fig. 11B) composed of a polysulfone hollow-fiber membrane to encapsulate genetically engineered human cells secreting GDNF [245–247], which remain stable for >1 year after implantation into the putamen of the brain in animal models and in clinical trials [248,249]. This device has the potential to deliver various cell-derived substances, alone or in combination, to the CNS. In the first half of 2015, an investigational new drug application was filed for a phase Ib trial in approximately 12 patients with PD to demonstrate its safety and feasibility.

AD is an irreversible and progressive brain disorder that mostly affects the older population. AD is the most prevalent form of adult onset dementia and is expected to affect 115 million individuals by 2050 [250]. AD is characterized by a progressive deterioration of cognitive and mnemonic abilities, which is at least partially related to the degeneration of basal forebrain cholinergic neurons. Although current therapies cannot prevent the loss of these neurons or the associated memory deficits, encapsulated nerve growth factor (NGF)-secreting baby hamster kidney (BHK) cells were shown to robustly induce the development of cholinergic fibers near the implant sites in rats and NHPs [249–252]. More recently, a better understanding of the roles of Aβ aggregates and neurofibrillary tangles in AD pathology has led to the development of anti-Aβ therapies to prevent or delay AD onset [253,254]. Macroencapsulation devices composed of hollow fibers were used to transplant myoblasts genetically engineered to release a single-chain variable antibody fragment directed against the N terminus of the Aβ peptide, resulting in reduced Aβ production and deposition and improvements in the associated behavioral deficits [255]. As the invasiveness of the procedure is a major obstacle towards clinical applications in presymptomatic AD patients, novel flat-sheet devices for subcutaneous implantation were developed, which also enable the volume of the transplanted cells to be increased [255]. These devices are composed of two porous polymer membranes enclosed in two mesh sheets for

mechanical stability and neovascularization. The inner chamber can contain up to several millions of myoblast cells that are loaded into the device via a dedicated port. Studies in mice have demonstrated that these subcutaneously implanted devices can release 50 μg/ml of anti-Aβ IgG antibody for 19 weeks [52], with ongoing investigations indicating that similar levels of monoclonal antibodies can be achieved for more than 10 weeks [255]. These results seem to validate the encapsulated cell therapy technology combined with myogenic cells for the long-term delivery of anti-Aβ monoclonal antibodies, leading to a significant reduction of the amyloid brain pathology in AD mouse models. Clinical studies (NCT01163825) for another encapsulation device for AD treatment, developed by NsGene (NsG0202), suggest that a sustained delivery of low doses of NGF to the cholinergic neurons of the basal forebrain could have clinical benefits regarding the progression and even prevention of AD [256–258].

4.3. Cancer

Immunotherapy refers to the modulation of the natural immune response in order to treat or prevent diseases, including cancer. Interestingly, studies in mice have found that endostatin-expressing fibroblasts cells in a subcutaneously implanted Theracyte™ immunoisolation device inhibited the growth of Ehrlich tumors and reduced melanoma growth by 42.4% [259–261]. These reports indicate that macroencapsulation is a promising platform for innovative therapeutic strategies in cancer treatment.

Recently, the biotechnology company MaxiVax SA (Switzerland) [262] designed a flat macroencapsulation device specifically for the subcutaneous implantation of cells that release granulocyte-macrophage colony-stimulating factor (GM-CSF) for the treatment of solid tumors [255]. The device ($27 \times 12 \times 1.2$ mm) is composed of two permeable membranes and a loading port for the injection of cells (Fig. 11C) and was tested in patients with various types of cancer, such as renal cell carcinoma, melanoma, prostate, lung, and pancreas cancer [262]. Clinical results show that GM-CSF released at the implantation site produces an effective antitumor immune response [263]. A new system from MaxiVax, named MVX-ONCO-1, is designed to combine the local delivery of GM-CSF with irradiated tumor cells from the patient [264]. The objective is to deliver tumor antigens and cytokines at the site of the cell injection to produce a local adjuvant vaccine effect [265]. The first phase I clinical study (NCT02193503) [266] targeted patients with a variety of solid tumors, including pancreatic, colon, head and neck, prostate, and ovarian tumors, and chordomas, which had failed standard therapies. The 8-week study, with 6 vaccine injections and 6 subcutaneous implantations of the immune booster, demonstrated that MVX-ONCO-1 was safe and well tolerated, with no occurrence of any serious adverse events or clinically significant local or systemic reactions [266]. The company is initiating a phase II clinical trial for head and neck cancer and other solid tumors.

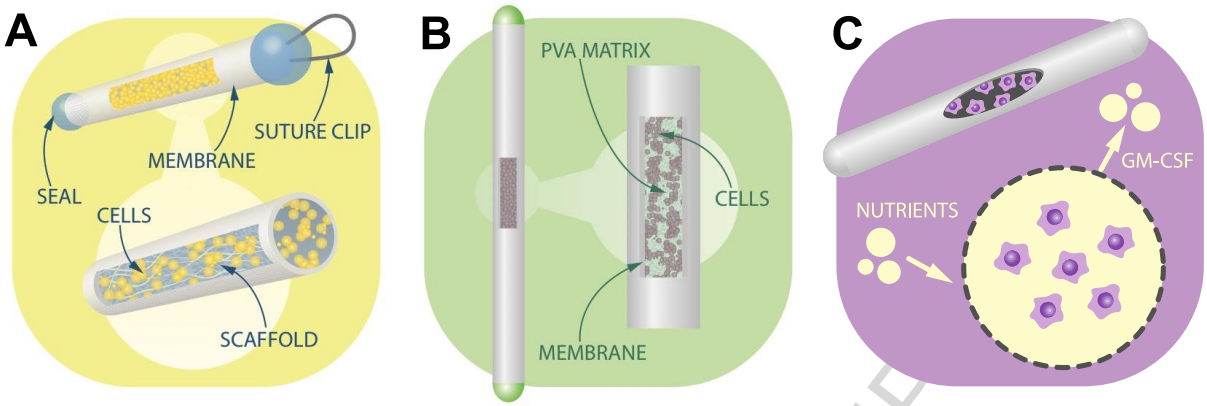

Figure 11: *(A) NTC-501 technology for chronic eye diseases, consisting of a semipermeable exterior capsule and internal scaffolding, enabling controlled cell growth and continuous protein release. (B) NsGene straw-like device that contains cells genetically modified to produce a therapeutic factor for implantation into the brains of patients. (C) MVX-ONCO-1 encapsulation device containing allogenic cells for the release of GM-CSF.*

4.4. Wound healing and regeneration

Chronic wounds affect approximately 2% of the world population, corresponding to 6.5 million patients, with a cost of $25 billion annually in the United States alone [267]. Venous leg ulcers, diabetic foot ulcers, and pressure ulcers are the most prevalent chronic nonhealing wounds. Among the several new treatment modalities for tissue regeneration, stem cell-based therapies have gained interest as a promising approach, demonstrating enhanced wound healing and increased blood vessel and granular tissue formation [268].

To protect and improve the regenerative potential of stem cells in a wound environment, various delivery systems have been developed. Among these, bioscaffolds, composed of collagen, hyaluronic acid, or other naturally derived or synthetic materials, have become popular for encapsulating stem cells [269–271]. Rustad *et al.* showed that seeding stem cells onto a pullulan collagen preserves their expression of stemness-related genes and significantly accelerates wound healing [272]. By geometrically and chemically altering porous scaffolds, a wide range of progenitor cell-based therapeutics has been evaluated. Moreover, scaffolds have been supplemented with growth factors, small molecules, and anti-inflammatory and/or antioxidant substances in order to modulate stem cell activity and wound healing capability [273]. These advanced materials play an important role in enhancing the survival and functionality of the encapsulated cells. For example, Apligraf® (Organogenesis Inc.) is an FDA-approved product for the treatment of venous and diabetic leg ulcers. This product consists of an extracellular matrix, allogenic dermal fibroblasts, and epidermal keratinocytes to provide growth factors and wound closure and a stratum corneum for mechanical strength and as a barrier to infections [274]. In 2012, Organogenesis Inc. also received FDA approval for GINTUIT™ (allogeneic cultured keratinocytes and fibroblasts in bovine collagen), an allogeneic cellularized scaffold (Fig. 12A) that promotes the generation of oral soft tissue in adults with mucogingival conditions. In 2014, this company acquired Dermagraft® (developed by Shire Pharmaceuticals [United Kingdom]), which is a tissue-engineered and FDA-approved product consisting of a dermal substitute generated by culturing neonatal dermal fibroblasts on a bioabsorbable polyglactin mesh scaffold [275]. In an extensive phase 3 clinical study (NCT01181440) [276], Dermagraft® promoted faster and more complete wound closure that in the control group.

4.5. Kidney failure

Every year, more than 200,000 people in the United States are affected by acute kidney injury and end-stage renal disease, with a mortality rate of approximately 50% [277]. Despite decades of efforts to develop novel renal replacement therapies, the morbidity and mortality associated with these disease states have remained unaltered [278]. While conventional treatment is focused mainly on organ removal, newer strategies such as cell therapy and cell processing aim to reduce the need for dialysis and transplantation. Some of the current applications involve the seeding of cells within implantable or external devices, such as hollow-fiber bioreactors, or encapsulating membranes [279,280].

The strategy adopted by Humes and colleagues at the University of Michigan is to administer cell therapy from an extracorporeal circuit, providing immunoisolation and enabling the use of allogeneic cells [281]. Their device, called a renal tubule assist device (RAD), is an external encapsulation system composed of polysulfone hollow fibers coated with collagen IV containing renal proximal tubule cells. In canine and porcine models, the RAD improved the regulation of plasma cytokine levels and cardiovascular performances, leading to increased survival times [282–284]. A phase I/II clinical trial on 10 patients showed that RAD therapy was safe over 24 hours and demonstrated the viability and functionality of the cells during the therapy, with a 50% reduction in the mortality rates. In a Phase II randomized open-label trial involving 58 patients with acute kidney injury at 12 clinical sites, RAD treatment increased the survival rate from 61% (patients treated with conventional continuous venovenous hemofiltration) to 33% of those patients treated with RAD by day 28 [277,285]. However, a follow-up phase IIb study was suspended due to the higher survival rate in patients treated with RAD without cells.

These unexpected findings led CytoPherx, Inc. (Ann Arbor, MI) to develop a new therapeutic device, called a selective cytopheretic device (SCD) [286,287]. The SCD comprises a synthetic membrane cartridge made with polysulfone fibers and a tubing system for connection with a standard continuous renal replacement therapy (CRRT) device. The SCD cartridge works as an immunomodulatory device, as it sequesters and inhibits activated leukocytes, thereby modulating the inflammation [278,288]. The safety of the SCD device was demonstrated in a phase IIa single-center study involving 12 patients [277]. The reported mortality of the control group was 78% compared to 22% for the SCD treatment group. A phase IIb multicenter U.S. pilot study involving 35 patients evaluated the safety and efficacy of the SCD treatment on patients requiring CRRT [288]. The results showed that the outcomes of patients treated with the SCD and CRRT were better than those receiving CRRT alone, with a reduced mortality rate on day 60 (31.4% versus 50%) [288]. In light of these results, an additional randomized trial was performed on 134 patients, in which 65 patients received SCD therapy (NCT01400893) [289]. Unfortunately, no significant difference in 60-day mortality was observed between the SCD group and the control [290].

Another encapsulation system for the controlled sustainable delivery of secreted factors via external dialysis is under development by Sentien Biotechnologies (Fig. 12B). This device, named SBI-101 (Sentinel™), which is now in a phase I/II clinical trial (NCT03015623) [291], contains MSCs seeded in an approved blood-filtration device in which blood flows through the hollow fibers and therapeutic factors can be delivered into the patient's blood without any leakage of the MSCs [292]. The efficacy of and pharmacodynamic responses to SBI-101 therapy will be evaluated in 24 patients that will be enrolled by the end of 2018. The SBI-101 offers two major advantages over traditional cell therapy administration. First, as the MSCs are housed in an extracorporeal device, the duration of therapeutic activity it significantly extended compared to that of traditional routes of MSC administration, such as injection or intravenous

infusion, where <1% of systemically administered MSCs persist for longer than a week following injection. Second, this device overcomes MSC dosage limitations that occur with injection or intravenous infusion.

A surgically implantable artificial kidney for people with end-stage kidney disease is under investigation by Drs. Shuvo Roy and William Fissell at UC San Francisco [293]. This artificial kidney comprises a silicon nanofilter embedded in microscopic scaffolding to filter the blood and human kidney tubule cells, which enables metabolic functioning and the reabsorption of water from the filtrate to control blood volume [294,295]. The artificial kidney is designed to be implanted near the patient's own kidneys and connected to the patient's blood supply and bladder. Clinical trials for the implantable artificial kidney are expected to begin in 2018.

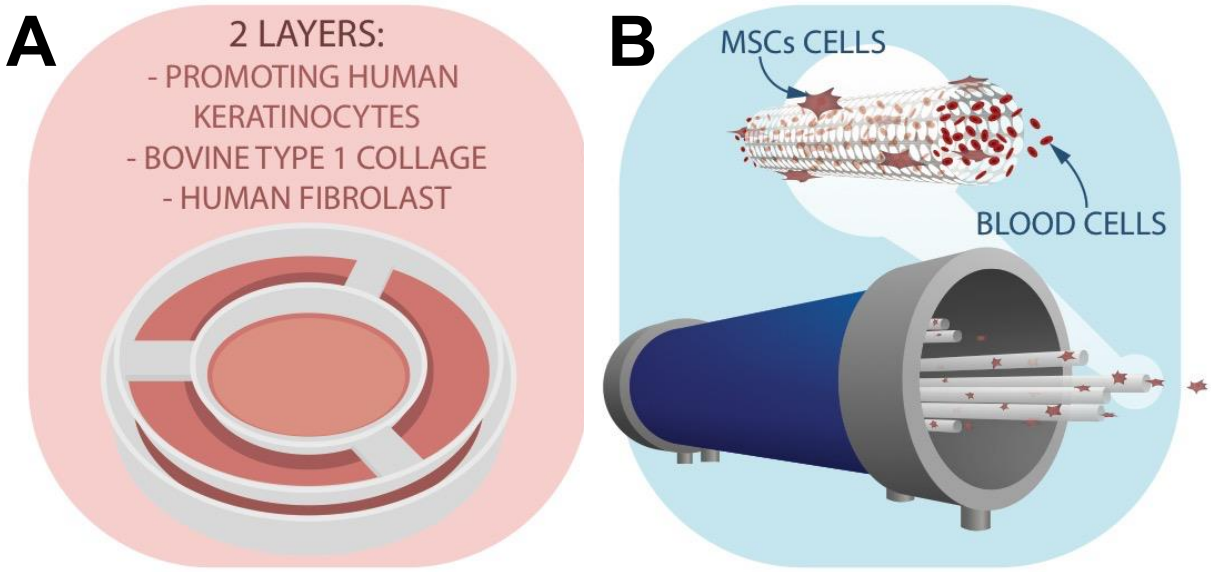

Figure 12: *(A) Schematic of GINTUIT™, a cellularized bioscaffold for wound regeneration consisting of allogeneic cultured keratinocytes and fibroblasts in bovine collagen. (B) Sentien SBI-101 technology in which MSCs are seeded in an extracorporeal device that delivers the factors they secrete to the patient's bloodstream.*

4.6. Cardiovascular diseases

Cardiovascular diseases, such as MI, stroke, and heart failure, are the leading causes of death worldwide [296]. As the damaged myocardium, as well as the noncontractile scar tissue, can significantly affect the proper functioning of the heart after MI and the regenerative capacity of endogenous cardiac tissue is limited, stem cell transplantation is being explored as a potential treatment. PSCs, including embryonic stem cells and iPSCs, demonstrate the capability to differentiate into functional cardiomyocytes [297–299]. Although there is concern for teratoma formation from PSCs, the administration of fully differentiated cardiomyocytes may not be useful, as they do not integrate well with host cardiomyocytes to function in a coordinated fashion. MSCs have been shown to promote angiogenesis [300], prevent apoptosis [300], modulate immune responses [301], recruit progenitor cells, and facilitate tissue remodeling [302] under such conditions. However, major challenges are the poor retention and survival of transplanted cells, as well as the adverse effects of inflammation and immunoreaction. the contractile nature of the myocardium mechanically disperses the transplanted cells, and the

avascular, hostile, and strong proinflammatory microenvironment after MI can damage them [303]. To address these challenges, various cell delivery and encapsulation strategies using natural or synthetic matrices, porous scaffolds, or cell sheets/patches are being investigated to improve cell retention and survival, as described below.

In a preclinical study by Levit *et al.* [44], hearts treated with encapsulated human MSCs retained the stem cells and showed improved revascularization and reduced scar formation, resulting in an improvement in left ventricular function as measured by transthoracic echocardiography and cardiac magnetic resonance imaging. Tang *et al.* [304] demonstrated that human cardiac stem cells encapsulated in thermosensitive poly(*N*-isopropylacrylamide-co-acrylic acid) nanogel and transplanted in mouse and pig models of MI preserved cardiac function and reduced the scar size. In another *in vivo* study, Chi *et al.* [305] demonstrated the potential for cardiac repair using bone marrow MSCs encapsulated in silk fibroin/hyaluronic acid patches in a rat model of MI. In 2002, Strauer *et al.* [306] demonstrated the potential of cell therapy in myocardial regeneration and neovascularization in a clinical study in which autologous mononuclear bone marrow cells were administered to the hearts of patients with MI. Since then, numerous clinical studies have investigated the safety and efficacy of different types of stem cells for cardiovascular applications, demonstrating their great promise [306–310]; however, issues related to long-term engraftment and the optimal cell type, dose, route, and administration strategies need to be resolved and the encapsulation strategies validated clinically to realize the full potential of stem cell therapy for cardiovascular diseases.

5. Key Challenges

In addition to the availability of good quality donor cells and appropriate delivery strategies, the determination of the optimal site for cell delivery is a matter of intense research. As described by *Pepper et al*. [311], the optimal site should have an adequate tissue volume capacity and, to prevent hypoxia events, should be in close proximity to vascular networks ensuring a sufficient oxygen supply to the graft. Moreover, that site should be easily accessible via minimally invasive methods to allow for cell transplantation, biopsy, and graft retrieval. Several other factors also should be considered, such as biocompatibility, safety, mechanical resistance, and the possibility of retransplantation.

Some groups attribute graft failure to the lack of direct vascularization, resulting in gradual tissue necrosis and death. Consequently, a site in which encapsulated islets are in contact with the bloodstream is obligatory for clinical applications. Although the peritoneal cavity has been investigated in several studies with encapsulated cells because of its accessibility and capacity to accommodate a large transplant volume, the optimal site for transplantation has yet to be determined. Despite the sufficient oxygen tension (20–40 mmHg) in subcutaneous tissue for pancreatic islet cell transplantation [168], the deployment of islets into an unmodified subcutaneous site has not been successful in reversing diabetes in either animal models or humans 147. Various strategies are emerging to prevascularize the chosen site before transplantation [311,312]. Thus, less vascularized sites, such as subcutaneous tissue, may become suitable for cell transplantation. Nevertheless, cell transplantation as a clinically viable approach to successfully treat diseases also entails the ability to monitor, retrieve, replace, and supplement the cells via simple and minimally invasive procedures. Numerous new cell delivery technologies and approaches are designed for subcutaneous transplantation with these requirements in mind.

Another critical limitation to the success of these therapies is the adverse tissue responses to the materials within the micro- and macroencapsulation systems [313–315]. For example, commercially available alginates can cause inflammatory responses due to their inherent

pathogen-associated molecular patterns [167]. Furthermore, many systems have been associated with cell protrusion, which can also lead to strong inflammatory responses, resulting in complete fibrosis of the capsules and necrosis of the transplanted cells. Mechanical properties might also be limiting factors. Different encapsulation systems are characterized by different elasticities and mechanical resistances, for which the optimal parameters are unknown and difficult to determine. The optimal properties of encapsulation systems are also recipient and site dependent. Although cell therapy offers great promise for the treatment of many medical conditions, with different types of cells of various sources being tested, concerns regarding their ethical use and regulatory challenges also need to be addressed.

6. Conclusions

Cell therapy and transplantation represent a vast research area. In this review, we presented only a subset of the current approaches, with an emphasis on the technologies that are at advanced stages of development, under clinical evaluation, or already FDA approved. Despite the several decades of intense research, it remains difficult to draw conclusions about which material or if micro- or macroencapsulation is most appropriate for clinical use. Recent research indicates that cell encapsulation systems are possible solutions for many endocrine disorders for which the minute-to-minute regulation of metabolites is mandatory and a structure similar to that of the native organ is important. More generally, it is likely that these technologies may play a significant role in the next generation of therapeutics. Drug delivery may ultimately be achieved and finely controlled by cells as opposed to the current modes of administration. This implies that drugs could be dosed exclusively when needed and at precise amounts in response to biological stimuli. It is clear that the scalability and clinical translation of these biotechnologies will depend on their cost-effectiveness as well as the establishment of strict regulatory aspects. Indeed, one of the major challenges involves moving from laboratory-based techniques to clinically acceptable large-scale practices operating under reproducible, safe, and high-output requirements.

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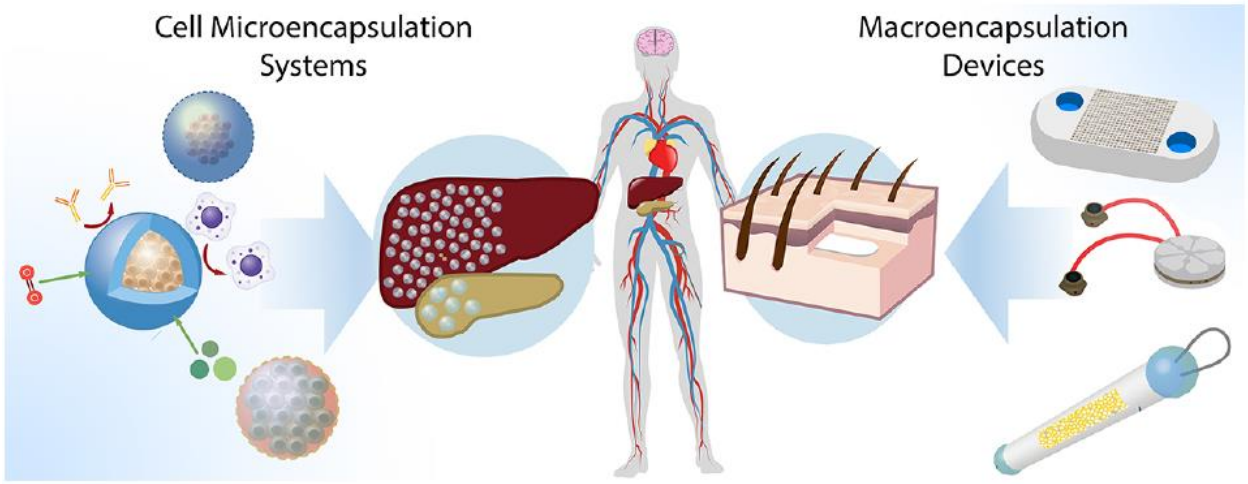

Graphical abstract